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 ********************************** *
WELCOME TO THE          * *     U.S. PA
TENT TEXT FILE       * ****************
***************
=> s (immunoglobulin or immunoglobin or ig)(w)fusion

      6968 IMMUNOGLOBULIN
       281 IMMUNOGLOBIN
      6055 IG
     39921 FUSION
L1       82 (IMMUNOGLOBULIN OR IMMUNOGLOBIN OR
IG)(W)FUSION
=> s l1(p)hcg

      1358 HCG
L2       0 L1(P)HCG

=> s fusion protein

     39921 FUSION
     60184 PROTEIN
L3    2942 FUSION PROTEIN
          (FUSION(W)PROTEIN)

=> s chimeric protein

      2907 CHIMERIC
     60184 PROTEIN
L4     308 CHIMERIC PROTEIN
          (CHIMERIC(W)PROTEIN)

=> s l3 or l4

L5     3093 L3 OR L4

=> s l5 and (tnf or cachectin or lymphotoxin)

      2241 TNF
       148 CACHECTIN
       350 LYMPHOTOXIN
L6     274 L5 AND (TNF OR CACHECTIN OR
LYMPHOTOXIN)

=> s l5(p)(tnf or cachectin or lymphotoxin)

      2241 TNF
       148 CACHECTIN
       350 LYMPHOTOXIN
L7      47 L5(P)(TNF OR CACHECTIN OR
LYMPHOTOXIN)

=> d kwic
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US PAT NO: 5,744,304 [IMAGE AVAILABLE] L7: 1 of 47
SUMMARY:

BSUM(8)

Other . . . have utilized gene therapy methods. For example, using gene transfer vectors in mice (Kolls et al., 1994), researchers constructed a **chimeric** **protein** capable of binding and neutralizing tumor necrosis factor (**TNF**). While the desired effect of producing high levels of constitutively produced **lymphotoxin** was achieved using this system, it was also reported that the animals were rendered highly susceptible to infection by Listeria. . .

DETDESC:

DETD(112)

Gene . . . non-replicating adenovirus (6.times.10.sup.12 plaque-forming units) or a DNA-liposome complex (10 mg DNA). The encoded antidote protein may be any of **TNF**-receptor-human immunoglobulin **fusion** **protein**, IL-10, fibrinogen, ACTH, or BPI. To provide multiple recombinant antidote proteins in vivo, more than one kind of vector-antidote protein. . .

=> d kwic 2

US PAT NO: 5,741,774 [IMAGE AVAILABLE] L7: 2 of 47
SUMMARY:

BSUM(12)

In . . . if the levels of cytokines that contribute to the deleterious effects associated with rheumatoid arthritis could be regulated. For example, **TNF** is believed to have a role in rheumatoid arthritis and administration of a soluble **TNF** receptor fused to an immunoglobulin Fc domain resulted delayed the onset of an experimentally induced arthritis and resulted in a less severe grade of arthritis in mice. This result suggests that such a **fusion** **protein** could be useful for reducing the severity of rheumatoid arthritis.

SUMMARY:

BSUM(13)

Unfortunately, a biological material such as a **TNF** receptor/Fc domain **fusion** **protein** can be expensive to prepare in a form that is sufficiently pure for use as a therapeutic agent. In addition, such a **fusion** **protein** can present "foreign" epitopes that may induce an undesirable immune response in the treated subject. Such an immune response can decrease the effective concentration of the agent in the treated subject by binding to the **fusion** **protein** and can be involved in the formation of immune complexes, which can have deleterious effects in the treated subject. Thus,. . .

=> d kwic 3

US PAT NO: 5,741,667 [IMAGE AVAILABLE] L7: 3 of 47
DRAWING DESC:

DRWD(10)

(A) The hTNF-R2 was immunoprecipitated from 293 and 293/**TNF**-R2 cells and incubated with lysates from .sup.35 S-labeled CT6 cells that had been preincubated with 50 .mu.l of the indicated GST-hTNF-R2icd **fusion** **protein** beads as competitor. Reactions were analyzed by SDS-PAGE and autoradiography. Arrows indicate bands of 45 to 50-56 kd and 68. . .
DRAWING DESC:

DRWD(13)

FIG. 8. Subcellular localization of **TNF**-R2 associated factors. Cytoplasmic and cell membrane fractions were

prepared from .sup.35 S-labeled CT6 cells as described in the text. These. . . SDS-Page and autoradiography. Arrows indicate bands of 45 to 50-56 kd and 68 kd that coprecipitate specifically with the GST-hTNF-R2icd **fusion** **protein**. Molecular weight markers are indicated on the right in kd.
DRAWING DESC:

DRWD(15)

Large scale purification of **TNF**-R2 associated factors from CT6 cells by GST-hTNF-R2icd **fusion** **protein** affinity chromatography was performed as described in the text. One tenth of the obtained material was analyzed by SDS-PAGE and. . . silver staining. Arrows indicate bands of 45 to 50-56 kd and 68-70 kd that were eluted specifically from the GST-hTNF-R2icd **fusion** **protein** affinity column. Molecular weight markers are indicated on the right in kd.

DRAWING DESC:

DRWD(29)

FIG. 16. Coprecipitation of GST-TRAF2 **fusion** **protein** in 293 cell extracts. GST and GST-TRAF2 **fusion** **protein** beads were incubated with lysates from 293 and 293TNF-R2 cells as described in the text. Reactions were analyzed by SDS-PAGE and Western blot analysis using anti-human **TNF**-R1 monoclonal antibody 986 (0.5 .mu.g/ml) and anti-human **TNF**-R2 monoclonal antibody 1036 (0.5 .mu.g/ml). An arrow indicates the 75-80 kd hTNF-R2 band that is coprecipitated specifically with the GST-TRAF2 **fusion** **protein**. Molecular weight markers are indicated on the right in kd.

DETDESC:

DETD(47)

A large-scale purification scheme for purifying factors that associate with the intracellular domain of **TNF**-R2 takes advantage of plasmid expression vectors that direct the synthesis of foreign polypeptides in E. coli as fusions with the. . . S-transferase (GST), as described by Smith, D. B. and Johnson, K. S., Gene 67 31-40 (1988). The intracellular domain of **TNF**-R2 is expressed as a **fusion** **protein** with GST in E. coli recombinant host cells, and can be purified from crude bacterial lysates by absorption on glutathione-agarose beads (Sigma). A cell lysate containing the factor(s) to be purified is then applied to a GST-**TNF**-R2 **fusion** **protein** affinity column. Protein(s) bound to the column is/are eluted, precipitated and isolated by SDS-PAGE under reducing conditions, and visualized by. . .

DETDESC:

DETD(213)

Preferably, . . . illustrated in the Examples hereinbelow. Large-scale production and purification of recombinant Glutathione-S-transferase (GST) fusion proteins comprising the cytoplasmic domains of **TNF**-R2, CD40 or LMP1 are performed as described in the Examples. For large-scale production of a recombinant TRAF protein, the corresponding. . . (Sigma) for radioactive labeling in vitro. The biochemical screening assay is performed in a robotic automated system in which the GST-**TNF**-R2 or/CD40 or/LMP1 **fusion** **protein** is coated into 96 well microtiterplates and the radioactively labeled TRAF protein added in the presence of various compounds. After. . . unbound TRAF protein and the captured radioactivity is counted. Inhibitors that prevent the interaction between the TRAF protein and the GST-**TNF**-R2/CD40/LMP1 **fusion** **protein** are identified by decreased captured radioactivity compared with control wells that lack added compounds.

DETDESC:

DETD(215)

Based upon their ability to specifically associate with the intracellular domain of **TNF**-R2, the TRAF molecules of the present invention can be used to purify **TNF**-R2, which, in turn, is useful in the treatment of various pathological conditions associated with the expression of **TNF**, such as endotoxic (septic) shock and rheumatoid arthritis (RA), either as a soluble **TNF**-R2 protein or in the form of an immunoglobulin **fusion** **protein**. The dose regimens effective in the treatment of these and other diseases can be determined by routine experimentation. CD40 and. . .

DETDESC:

DETD(238)

In . . . procedure for factors that associate with the hTNF-R2icd, the intracellular domain of hTNF-R2 was expressed as a glutathione S-transferase (GST) **fusion** **protein** [Smith & Johnson, 1988, supra]. The intracellular domain of hTNF-R2 was amplified from pRK-**TNF**-R2 by PCR with Pfu DNA polymerase as described above using the oligonucleotide primers 5 '-GATCGGATCCAAAAAGAAGCC CTTGTGCCTGCA-3' (SEQ. ID NO: 31). . . beads were collected by brief centrifugation at 500.times.g and washed extensively with resuspension buffer. An aliquot of the purified GST-hTNF-R2icd **fusion** **protein** was analyzed by SDS-PAGE (FIG. 3). Concentrations of 5-8 mg **fusion** **protein**/ml of swollen beads were obtained routinely.

DETDESC:

DETD(242)

In addition, the GST-hTNF-R2icd(384-424) **fusion** **protein** was able to coprecipitate the bands at 45 to 50-56 kd and 68 kd although to a weaker extent than the other fusion proteins (FIG. 5). The 41 amino acids of the hTNF-R2icd contained in this GST-**fusion** **protein** are comprised within the 78 amino acids region the hTNF-R2icd that has been identified to be required for mediating **TNF** signaling in CT6 cells (see above). This suggests that this short region of the hTNF-R2icd is sufficient to mediate the. . .

DETDESC:

DETD(243)

Competition coprecipitation experiments were performed in which the hTNF-R2 was immunoprecipitated from unlabeled 293/**TNF**-R2 cells and then incubated with labeled CT6 cell lysate that had been precleared with 50 .mu.l of GST-hTNF-R2icd **fusion** **protein** beads. Preincubation of the CT6 extracts with GST beads alone or GST-hTNF-R2icd(-37) and GST-hTNF-R2icd(-59) **fusion** **protein** beads had no effect on the pattern of proteins coprecipitating with the immunoprecipitated hTNF-R2 (FIG. 6). However, if the cell lysate had been precleared with GST-hTNF-R2icd or GST-hTNF-R2icd(-16) **fusion** **protein** beads, these proteins did not coprecipitate with the

immunoprecipitated hTNF-R2 (FIG. 6), indicating that they had been depleted from the labeled CT6 cell extract by the GST-hTNF-R2icd fusion proteins. This result demonstrates that the wild type GST-hTNF-R2icd **fusion** **protein** associates with the same intracellular factors as the immunoprecipitated hTNF-R2. Consequently, this GST-**fusion** **protein** material can be used for large scale purification of factors that are associated with the intracellular domain the of hTNF-R2.. . . coprecipitating proteins very similar in size to the pattern observed with murine CT6 lysates (FIG. 7). This suggests that the **TNF**-R2 associated factors are closely related between the mouse and human species.

DETDESC:

DETD(270)

An expression vector encoding a GST-TRAF2 **fusion** **protein** was constructed. The TRAF2 coding region was amplified from pPC86TRAF2 by PCR with Pfu DNA polymerase as described above using. . . fragment was blunt-ended using E. coli DNA polymerase I, digested with BamHI and cloned into BamHI/SmaI-digested pGEX-2TK vector. The GST-TRAF2 **fusion** **protein** was expressed in the presence of 1 mM ZnCL.sub.2 and purified as described above. GST and GST-TRAF2 **fusion** **protein** beads were incubated with lysates from 293 and 293/**TNF**-R2 cells, and analyzed by SDS-PAGE and Western blot analysis [Sambrook et al., "Molecular Cloning: A Laboratory Manual. Cold Spring Harbor. . . the secondary sheep anti-mouse horseradish peroxidase conjugate (Amersham) at a dilution of 1:6000. As shown in FIG. 16, the GST-TRAF2 **fusion** **protein** coprecipitates the hTNF-R2 in 293 cell extracts, thus confirming the results obtained from two hybrid analysis.

DETDESC:

DETD(272)

Cotransformation of pPC86TRAF1 into HF7c cells with the GAL4 DNA-binding **TNF**-R2 fusion constructs encoding the wild type human and murine intracellular domains indicated that the direct interaction between TRAF1 and the intracellular domain of **TNF**-R2 is weak (Table 2). However, cotransformation of pPC97TRAF1 and pPC86TRAF2 or pPC97TRAF2 and pPC86TRAF1 revealed that TRAF1 and TRAF2 interact. . . each other (Table 2) suggesting that a heterodimeric complex of TRAF1 and TRAF2 is associated with the intracellular domain of **TNF**-R2. Subsequently yeast vectors were constructed in which TRAF2 is expressed directly, i.e. not as a GAL4 **fusion** **protein**. pPC97TRAF2 was digested with HindIII and SalI to release a 0.5 kb DNA fragment encoding the GAL4 DNA-binding domain, end-filled. . . cells (Table 3). This result confirms that a heterodimeric complex of TRAF1 and TRAF2 interacts with the intracellular domain of **TNF**-R2. In this protein complex mainly TRAF2 contacts the receptor directly potentially through interaction of its RING finger domain with the C-terminal region of the intracellular domain comprising amino acids 304-345 of the human **TNF**-R2 as suggested from mutational analysis and coprecipitation experiments (see above). TRAF1 and TRAF2 can also form homodimeric complexes as shown. . .

DETDESC:

DETD(279)

TABLE 3

Interaction between TRAF1, TRAF2 and the Intracellular Domain of **TNF**-R2
(continued)

Transformant		
Activation-domain	Growth on trp-- DNA-binding domain hybrid	
hybrid	Direct expression	
	leu.sup.-	his.sup.- medium
GAL4(DB)	GAL4(TA)-TRAF1. . . plasmids (see text) encodin the indicated GAL4 DNAbinding domain (DB) fusion proteins, the GAL4 transcriptional activation domain (TA) TRAF1 **fusion** **protein**, and TRAF2 or TRAF2 fused to the simian virus 40 large tumor antigen nuclear localization signal (NLS). The final. . .	

DETDESC:

DETD(282)

To . . . within the TRAF2 protein that are required for homodimerization, heterodimerization with TRAF1 and for interaction with the cytoplasmic domain of **TNF**-R2 GAL4-TRAF2 **fusion** **protein** vectors were constructed which express mutant TRAF2 proteins. A 1.9 kb DNA fragment which encodes amino acids 87-501 of TRAF2. . . table 4 indicate that the RING finger domain of TRAF2 is not required for interaction with the cytoplasmic domain of **TNF**-R2 since the mutant TRAF2 protein in which the RING finger domain (amino acids 1-86) was removed was still able to associate with the cytoplasmic domain of **TNF**-R2. Also, this mutant TRAF2 protein could still associate with both TRAF1 and wild-type TRAF2. The same results were obtained for. . . mediate homo- and heterodimerization of TRAF1 and TRAF2 as well as for interaction of TRAF2 with the cytoplasmic domain of **TNF**-R2.
=> d 4-14

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5. 5,723,437, Mar. 3, 1998, CD6 ligand; Barton F. Haynes, et al., 514/2; 435/69.1; 530/350, 413 [IMAGE AVAILABLE]

6. 5,721,121, Feb. 24, 1998, Mammalian cell culture process for producing a tumor necrosis factor receptor immunoglobulin chimeric protein; Tina Etcheverry, et al., 435/69.7, 325, 328, 358, 361; 530/387.3, 395 [IMAGE AVAILABLE]

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8. 5,712,381, Jan. 27, 1998, MADD, a TNF receptor death domain ligand protein; Lih-Ling Lin, et al., 536/23.5; 435/69.1, 70.1, 320.1, 325; 530/300, 350 [IMAGE AVAILABLE]

9. 5,712,155, Jan. 27, 1998, DNA encoding tumor necrosis factor-.alpha. and -.beta. receptors; Craig A. Smith, et al., 435/320.1; 424/85.1; 435/69.3, 69.5; 530/351, 388.23, 389.2; 536/23.1; 935/12 [IMAGE AVAILABLE]

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435/69.1, 252.3, 320.1; 536/23.5 [IMAGE AVAILABLE]

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13. 5,698,195, Dec. 16, 1997, Methods of treating rheumatoid arthritis using chimeric anti-TNF antibodies; Junming Le, et al., 424/133.1, 141.1, 142.1, 145.1; 514/825; 530/351, 387.3, 388.1, 388.23 [IMAGE AVAILABLE]
14. 5,688,656, Nov. 18, 1997, Cytokine-induced marker for inflammatory response; Vishva M. Dixit, 435/7.21, 69.1; 436/518, 536; 530/388.23, 389.2, 395 [IMAGE AVAILABLE]

=> d 15-24

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17. 5,674,704, Oct. 7, 1997, Cytokine designated 4-IBB ligand; Raymond G. Goodwin, et al., 435/69.1, 320.1; 530/350; 536/23.5 [IMAGE AVAILABLE]
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19. 5,656,272, Aug. 12, 1997, Methods of treating TNF-.alpha.-mediated Crohn's disease using chimeric anti-TNF antibodies; Junming Le, et al., 424/133.1, 139.1, 145.1; 435/69.1, 69.6, 69.7; 530/387.3, 388.23 [IMAGE AVAILABLE]

20. 5,650,150, Jul. 22, 1997, Recombinant antibody cytokine fusion proteins; Stephen D. Gillies, 424/134.1, 85.1, 133.1; 435/69.7 [IMAGE AVAILABLE]

21. 5,643,570, Jul. 1, 1997, BPI-immunoglobulin fusion proteins; Georgia Theofan, et al., 424/134.1; 435/69.1, 172.3, 252.3, 320.1; 530/387.3; 536/23.4 [IMAGE AVAILABLE]

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24. 5,629,285, May 13, 1997, Inhibitors of TNF-.alpha. secretion; Roy A. Black, et al., 514/2, 7, 119, 507, 563; 530/331 [IMAGE AVAILABLE]
=> d 25-34

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=> d 35-44

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36. 5,506,340, Apr. 9, 1996, Tumor necrosis factor inhibitors; George A. Heavner, 530/324, 325, 326, 327, 328, 329, 330 [IMAGE AVAILABLE]
37. 5,486,595, Jan. 23, 1996, Tumor necrosis factor inhibitors; George A. Heavner, 530/324, 325, 326, 327, 328, 329, 330 [IMAGE AVAILABLE]
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factor-.alpha. and -.beta. receptors; Craig A. Smith, et al., 435/365; 424/85.1; 435/69.4, 172.3; 530/351, 388.23; 536/23.51 [IMAGE AVAILABLE]
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44. 5,359,039, Oct. 25, 1994, Isolated poxvirus A53R-equivalent tumor necrosis factor antagonists; Craig A. Smith, et al., 530/350; 424/186.1, 232.1; 530/826; 536/23.72; 930/220 [IMAGE AVAILABLE]

=> d kwic 41

US PAT NO: 5,434,131 [IMAGE AVAILABLE] L7: 41 of 47
DETDESC:

DETD(37)

In one embodiment, the CTLA4Ig **fusion** **protein** or CTLA4Ig/CD28Ig hybrid proteins, may be introduced in a suitable pharmaceutical carrier in vivo, i.e. administered-into a human subject for treatment of pathological conditions such as immune system diseases or cancer. Introduction of the **fusion** **protein** in vivo is expected to result in interference with T cell interactions with other cells, such as B cells, as. . . cell interactions may result in decreased T cell activity, for example, decreased T cell proliferation. In addition, administration of the **fusion** **protein** in vivo is expected to result in regulation of in vivo levels of cytokines, inciuding, but not limited to, interleukins,. . . IL-4, IL-6, IL-8, growth factors including tumor growth factor ("TGF"), colony stimulating factor ("CSF"), interferons ("IFNs"), and tumor necrosis factor ("**TNF**") to promote desired effects in a subject. For example, when the **fusion** **protein** is introduced in vivo, it may block production of cytokines, which contribute to malignant growth, for example of tumor cells. The **fusion** **protein** may also block proliferation of viruses dependent on T cell activation, such as the virus that causes AIDS, HTLV1.
=> d kwic 42

US PAT NO: 5,395,760 [IMAGE AVAILABLE] L7: 42 of 47
DETDESC:

DETD(71)

Recombinant human **TNF**.alpha., in the form of a **fusion** **protein** containing a hydrophilic octapeptide at the N-terminus, was expressed in yeast as a secreted protein and purified by affinity chromatography (Hopp et al., Bio/Technology 6:1204, 1988). Purified recombinant human **TNF**.beta. was purchased from R & D Systems (Minneapolis, Minn.). Both proteins were radiolabeled using the commercially available solid phase agent,. . . 20 .mu.l (2 mCi) Na .sup.125 I. This solution was then transferred to a second glass tube containing 5 .mu.g **TNF**.alpha. (or **TNF**.beta.) in 45 .mu.l PBS for 20 minutes at 4.degree. C. The reaction mixture was fractionated by gel filtration on a. . . serum albumin (BSA), 0.2% (w/v) sodium azide and 20 mM Hepes pH 7.4 (binding medium). The final pool of .sup.125 I-**TNF** was diluted to a working stock solution of 1.times.10.sup.-7 M in binding medium and stored for up to one month at 4.degree. C. without detectable loss of receptor binding activity. The specific activity is routinely 1.times.10.sup.6 cpm/mmole **TNF**.

=> d ab 42

US PAT NO: 5,395,760 [IMAGE AVAILABLE] L7: 42 of 47
ABSTRACT:
Tumor necrosis factor receptor proteins, DNAs and expression vectors encoding TNF receptors, and processes for producing TNF receptors as products of recombinant cell culture, are disclosed.

=> d ab kwic 40

US PAT NO: 5,447,851 [IMAGE AVAILABLE] L7: 40 of 47
ABSTRACT:
The invention relates generally to DNA sequences encoding chimeric polypeptides comprising extracellular portions of cytokine receptor polypeptides attached to a sequence encoding portions of IgG polypeptides. The invention relates generally, as well, to DNA sequences encoding chimeric polypeptides comprising extracellular portions of cytokine receptor polypeptides attached through oligomers encoding specifically cleavable peptide linkers to a sequence encoding portions of IgG heavy chain polypeptides More specifically, the invention relates to a construction in which a cDNA sequence encoding the extracellular domain of the human 55 kD TNF receptor is attached through an oligomer encoding a thrombin-sensitive peptide linker to a sequence encoding the F.sub.c portion and hinge region of a mouse IgGI heavy chain. The invention relates as well to uses of the chimeric polypeptide, including: use as a reagent for the antagonism and assay of TNF and lymphotoxin from diverse species; use as a means of determining the mechanism by which TNF, or analogs thereof, interacts with the TNF receptor; use as an antitumor reagent, particularly against placental tumors; and, use as a reagent capable of controlling birth.

SUMMARY:

BSUM(28)

In order to overcome at least some of the limitations of the prior art, the present invention discloses a **chimeric** **protein** in which the extracellular domain of a cytokine receptor, which normally engages the cytokine molecule, is covalently linked to an IgG molecule. In particular, and by way of example, a **TNF** receptor extracellular polypeptide is coupled to the CH.sub.2 through CH.sub.3 regions of a mouse IgGI heavy chain. Interposed between the. . . protease or other peptide cleaving reagent. In a particular embodiment, a hexapeptide sensitive to cleavage by thrombin is used. The **chimeric** **protein** is expressed and secreted by CHO cells. In another embodiment, the insect cell lines SF9 and SF21 may be used. . . hooked up to the chimeric polypeptide. Whichever vector/host system is utilized, the resulting recombinant chimera is highly active as a **TNF** inhibitor, is readily purified by affinity chromatography using an anti-mouse IgG or Protein A column, and is quantitatively cleaved by. . .

=> xxxxxxxxxxxxx

'XXXXXXXXXXXXX' IS NOT A RECOGNIZED COMMAND

=> d ab kwic 40

US PAT NO: 5,447,851 [IMAGE AVAILABLE] L7:

40 of 47
ABSTRACT:
The invention relates generally to DNA sequences encoding chimeric polypeptides comprising extracellular portions of cytokine receptor polypeptides attached to a sequence encoding portions of IgG polypeptides. The invention relates generally, as well, to DNA sequences encoding chimeric polypeptides comprising extracellular portions of cytokine receptor polypeptides attached through oligomers encoding specifically cleavable peptide linkers to a sequence encoding portions of IgG heavy chain polypeptides More specifically, the invention relates to a construction in which a cDNA sequence encoding the extracellular domain of the human 55 kD TNF receptor is attached through an oligomer encoding a thrombin-sensitive peptide linker to a sequence encoding the F.sub.c portion and hinge region of a mouse IgGI heavy chain. The invention relates as well to uses of the chimeric polypeptide, including: use as a reagent for the antagonism and assay of TNF and lymphotoxin from diverse species; use as a means of determining the mechanism by which TNF, or analogs thereof, interacts with the TNF receptor; use as an antitumor reagent, particularly against placental tumors; and, use as a reagent capable of controlling birth.

SUMMARY:

BSUM(28)

In order to overcome at least some of the limitations of the prior art, the present invention discloses a **chimeric** **protein** in which the extracelluiar domain of a cytokine receptor, which normally engages the cytokine molecule, is covalently linked to an IgG molecule. In particular, and by way of example, a **TNF** receptor extracellular polypeptide is coupled to the CH.sub.2 through CH.sub.3 regions of a mouse IgGI heavy chain. Interposed between the. . . protease or other peptide cleaving reagent. In a particular embodiment, a hexapeptide sensitive to cleavage by thrombin is used. The **chimeric** **protein** is expressed and secreted by CHO cells. In another embodiment, the insect cell lines SF9 and SF21 may be used. . . hooked up to the chimeric polypeptide. Whichever vector/host system is utilized, the resulting recombinant chimera is highly active as a **TNF** inhibitor, is readily purified by affinity chromatography using an anti-mouse IgG or Protein A column, and is quantitatively cleaved by. . .

=> d ab kwic 37

US PAT NO: 5,486,595 [IMAGE AVAILABLE] L7:
37 of 47
ABSTRACT:
Peptides which consist of 4-25 amino acids and which bind to tumor necrosis factor-alpha, prevent tumor necrosis factor-alpha from binding to its receptors and inhibit tumor necrosis factor-alpha activity are disclosed. Methods of inhibiting tumor necrosis factor-alpha activity and of treating individuals suffering from tumor necrosis factor-alpha-mediated diseases and disorders are disclosed.
DETDESC:

DETD(19)

In order to determine whether a peptide inhibits **TNF**.alpha., one or more of several assays may be performed. Included among these are assays which measure the ability a **TNF**.alpha. inhibitor candidate, i.e. a test compound, to inhibit **TNF**.alpha. from binding to a **fusion** **protein** that is composed of a **TNF** receptor or a **TNF**.alpha.-binding portion thereof, fused to an immunoglobulin molecule or a portion thereof. In other assays, the ability a test compound to inhibit **TNF**.alpha. from binding to an isolated **TNF** receptor is measured. Other assays include those which the ability of a **TNF**.alpha. inhibitor candidate, i.e. a test compound, to inhibit **TNF**.alpha. activity when **TNF**.alpha. is contacted with cells that react to the presence of **TNF**.alpha.. For example, **TNF**.alpha. is cytotoxic to some cells, such as WEHI cells, and assays can be used to measure the ability a test compound, to inhibit **TNF**.alpha. cytotoxicity.

DETDESC:

DETD(117)

In order to screen compounds for their ability to block **TNF**.alpha. binding to the **TNF** p55 receptor, an assay has been designed using **TNF**.alpha. and a p55/IgG **fusion** **protein** in place of monovalent, non-fusion p55 **TNF** receptor protein. This assay was designed to identify peptides which bind to human **TNF**.alpha. and thereby prevent the capture of the **TNF**.alpha. by a microtiter plate coated with p55-Ig **fusion** **protein**. A constant concentration of human **TNF**.alpha. is preincubated with the test peptide and then incubated on the p55-Ig coated microtiter wells. Bound **TNF**.alpha. is detected using a specific antisera and an alkaline phosphatase-conjugated probe. An active peptide will reduce the amount of human **TNF**.alpha. bound to the well relative to control wells in which **TNF**.alpha. but no peptide was added.

DETDESC:

DETD(118)

A 96-well, U-bottom polyvinylchloride microtiter plate was coated with 50 .mu.l/well of p55-Ig **fusion** **protein** at 5 .mu.g/ml in 0.01M sodium phosphate, 0.15M sodium chloride (PBS) by incubation overnight at 4.degree. C. or 2 hours at 37.degree. C. The **fusion** **protein**, which consists of a p55 **TNF** receptor protein portion and an IgG portion, can be produced as disclosed in U.S. application Ser. No. 08/010,406 filed Jan.. . .

=> d ab kwic 37

US PAT NO: 5,486,595 [IMAGE AVAILABLE] L7:
37 of 47
ABSTRACT:
Peptides which consist of 4-25 amino acids and which bind to tumor necrosis factor-alpha, prevent tumor necrosis factor-alpha from binding to its receptors and inhibit tumor necrosis factor-alpha activity are disclosed. Methods of inhibiting tumor necrosis factor-alpha activity and of treating individuals suffering from tumor necrosis factor-alpha-mediated diseases and disorders are disclosed.
DETDESC:

DETD(19)

In order to determine whether a peptide inhibits **TNF**.alpha., one or more of several assays may be performed. Included among these are assays which measure the ability a **TNF**.alpha. inhibitor candidate, i.e. a test compound, to inhibit **TNF**.alpha. from binding to a **fusion** **protein** that is composed of a **TNF** receptor or

a
TNF.alpha.-binding portion thereof, fused to an immunoglobulin molecule or a portion thereof. In other assays, the ability a test compound to inhibit **TNF**.alpha. from binding to an isolated **TNF** receptor is measured. Other assays include those which the ability of a **TNF**.alpha. inhibitor candidate, i.e. a test compound, to inhibit **TNF**.alpha. activity when **TNF**.alpha. is contacted with cells that react to the presence of **TNF**.alpha.. For example, **TNF**.alpha. is cytotoxic to some cells, such as WEHI cells, and assays can be used to measure the ability a test compound, to inhibit **TNF**.alpha. cytotoxicity.

DETDESC:

DETD(117)

In order to screen compounds for their ability to block **TNF**.alpha. binding to the **TNF** p55 receptor, an assay has been designed using **TNF**.alpha. and a p55/IgG **fusion** **protein** in place of monovalent, non-fusion p55 **TNF** receptor protein. This assay was designed to identify peptides which bind to human **TNF**.alpha. and thereby prevent the capture of the **TNF**.alpha. by a microtiter plate coated with p55-Ig **fusion** **protein**. A constant concentration of human **TNF**.alpha. is preincubated with the test peptide and then incubated on the p55-Ig coated microtiter wells. Bound **TNF**.alpha. is detected using a specific antisera and an alkaline phosphatase-conjugated probe. An active peptide will reduce the amount of human **TNF**.alpha. bound to the well relative to control wells in which **TNF**.alpha. but no peptide was added.

DETDESC:

DETD(118)

A 96-well, U-bottom polyvinylchloride microtiter plate was coated with 50 .mu.l/well of p55-Ig **fusion** **protein** at 5 .mu.g/ml in 0.01M sodium phosphate, 0.15M sodium chloride (PBS) by incubation overnight at 4.degree. C. or 2 hours at 37.degree. C. The **fusion** **protein**, which consists of a p55 **TNF** receptor protein portion and an IgG portion, can be produced as disclosed in U.S. application Ser. No. 08/010,406 filed Jan.. . .

=> d ab kwic 27

US PAT NO: 5,605,690 [IMAGE AVAILABLE] L7: 27 of 47
ABSTRACT:
A method for treating TNF-dependent inflammatory diseases in a mammal by administering a TNF antagonist, such as soluble TNFR.

DETDESC:

DETD(24)

A . . . a single chimeric antibody molecule having TNFR displayed bivalently. Such polyvalent forms of TNFR may have enhanced binding affinity for **TNF** ligand. One specific example of a TNFR/Fc **fusion** **protein** is disclosed in SEQ ID NO:3 and SEQ ID NO:4. Additional details relating to the construction of such chimeric antibody. . .
=> d ab kwic 22

US PAT NO: 5,641,751 [IMAGE AVAILABLE] L7: 22 of 47
ABSTRACT:
Peptides which consist of 4-25 amino acids and which bind to tumor necrosis factor-alpha, prevent tumor necrosis factor-alpha from binding to its receptors and inhibit tumor necrosis factor-alpha activity are disclosed. Methods of inhibiting tumor necrosis factor-alpha activity and of treating individuals suffering from tumor necrosis factor-alpha-mediated diseases and disorders are disclosed.
SUMMARY:

BSUM(44)

In order to determine whether a peptide inhibits **TNF**.alpha., one or more of several assays may be performed. Included among these are assays which measure the ability a **TNF**.alpha. inhibitor candidate, i.e. a test compound, to inhibit **TNF**.alpha. from binding to a **fusion** **protein** that is composed of a **TNF** receptor or a
TNF.alpha.-binding portion thereof, fused to an immunoglobulin molecule or a portion thereof. In other assays, the ability a test compound to inhibit **TNF**.alpha. from binding to an isolated **TNF** receptor is measured. Other assays include those which the ability of a **TNF**.alpha. inhibitor candidate, i.e. a test compound, to inhibit **TNF**.alpha. activity when **TNF**.alpha. is contacted with cells that react to the presence of **TNF**.alpha.. For example, **TNF**.alpha. is cytotoxic to some cells, such as WEHI cells, and assays can be used to measure the ability a test compound, to inhibit **TNF**.alpha. cytotoxicity.

DETDESC:

DETD(3)

In order to screen compounds for their ability to block **TNF**.alpha. binding to the **TNF** p55 receptor, an assay has been designed using **TNF**.alpha. and a p55/IgG **fusion** **protein** in place of monovalent, non-fusion p55 **TNF** receptor protein. This assay was designed to identify peptides which bind to human **TNF**.alpha. and thereby prevent the capture of the **TNF**.alpha. by a microtiter plate coated with p55-Ig **fusion** **protein**. A constant concentration of human **TNF**.alpha. is preincubated with the test peptide and then incubated on the p55-Ig coated microtiter wells. Bound **TNF**.alpha. is detected using a specific antisera and an alkaline phosphatase-conjugated probe. An active peptide will reduce the amount of human **TNF**.alpha. bound to the well relative to control wells in which **TNF**.alpha. but no peptide was added.

DETDESC:

DETD(4)

A 96-well, U-bottom polyvinylchloride microtiter plate was coated with 50 .mu.l/well of p55-Ig **fusion** **protein** at 5 .mu.g/ml in 0.01M sodium phosphate, 0.15M sodium chloride (PBS) by incubation overnight at 4.degree. C. or 2 hours at 37.degree. C. The **fusion** **protein**, which consists of a p55 **TNF** receptor protein portion and an IgG portion, can be produced as disclosed in U.S. application Ser. No. 08/010,406 filed Jan.. . .

=> d ab kwic 20

US PAT NO: 5,650,150 [IMAGE AVAILABLE] L7: 20 of 47
ABSTRACT:
Immunoconjugates for the selective delivery of a cytokine to a target cell are disclosed. The fusion proteins are comprised of an immunoglobulin heavy chain having a specificity for the target cell, such as a cancer or virus-infected cell, and a cytokine, such as lymphotoxin, tumor necrosis factor alpha, interleukin-2, or granulocyte-macrophage colony stimulating factor, joined via its amino terminal amino acid to the carboxy-terminus of the immunoglobulin. Nucleic acid sequences encoding these fusion proteins and methods of their preparation by genetic engineering techniques are also disclosed.

SUMMARY:

BSUM(6)

Another potential problem with expressing proteins, such as the lymphokine LT, as a **fusion** **protein** to an immunoglobulin chain is that the native molecule exists in solution as a trimer and binds more efficiently to. . . amino terminus is required for receptor binding activity. In fact, it has been postulated that the amino and carboxy-termini of **TNF**.varies., and, by analogy, LT, together form a structure that is required for receptor interaction.

DETDESC:

DETD(49)

Ig/**TNF** immunoconjugates were made by fusing nucleotide sequences encoding **TNF**.alpha. and immunoglobulin heavy chain such that **TNF**.alpha. is fused to the carboxy terminus of the heavy chain. Briefly, the mature **TNF**.alpha. coding sequence was fused to the end of the human C.gamma.1 CH3 exon using oligonucleotides. The recombined fragment was joined. . . selected as described above. Clones secreting human antibody determinants were expanded and used for the production and purification of the ch14.18-CH3-**TNF**.alpha. **fusion** **protein** by protein A Sepharose chromatography. The activity of the **fusion** **protein** was tested as described above for the CH3-LT fusion proteins.
DETDESC:

DETD(50)

As seen in FIG. 10, the amount of cytotoxicity obtained with the **fusion** **protein** met or exceeded that of native **TNF**.alpha. at either early (20 hr) or late (24 hr) points in the assay. This **fusion** **protein** appears to be fully functional with respect to **TNF**.alpha. activity, even though it was purified using protein A Sepharose. The CH3-LT construct was partially inactivated by the elution at. . .
=> d ab kwic 9

US PAT NO: 5,712,155 [IMAGE AVAILABLE] L7: 9 of 47
ABSTRACT:
Tumor necrosis factor receptor DNAs and expression vectors encoding TNF receptors, and processes for producing TNF receptors as products of recombinant cell culture, are disclosed.

DETDESC:

DETD(71)

A. Radiolabeling of **TNF**.alpha. and **TNF**.beta.. Recombinant human **TNF**.alpha., in the form of a **fusion** **protein** containing a hydrophilic octapeptide at the N-terminus, was expressed in yeast as a secreted protein and purified by affinity chromatography (Hopp et al., Bio/Technology 6:1204, 1988). Purified recombinant human **TNF**.beta. was purchased from R&D Systems (Minneapolis, Minn.). Both proteins were radiolabeled using the commercially available solid phase agent, IODO-GEN (Pierce).. . . 20 .mu.l (2 mCi) Na .sup.125 I. This solution was then transferred to a second glass tube containing 5 .mu.g **TNF**.alpha. (or **TNF**.beta.) in 45 .mu.l PBS for 20 minutes at 4.degree. C. The reaction mixture was fractionated by gel filtration on a. . . serum albumin (BSA), 0.2% (w/v) sodium azide and 20 mM Hepes pH 7.4 (binding medium). The final pool of .sup.125 I-**TNF** was diluted to a working stock solution of 1.times.10.sup.-7 M in binding medium and stored for up to one month at 4.degree. C. without detectable loss of receptor binding activity. The specific activity is routinely 1.times.10.sup.6 cpm/mmole **TNF**.

=> d ab kwic 7,6,2,1

US PAT NO: 5,716,805 [IMAGE AVAILABLE] L7: 7 of 47
ABSTRACT:
There is disclosed a method of preparing a soluble mammalian protein by culturing a host cell transformed or transfected with an expression vector encoding a fusion protein comprising a zipper domain and a heterologous mammalian protein.

DETDESC:

DETD(2)

The . . . of preparing a soluble mammalian protein by culturing a host cell transformed or transfected with an expression vector encoding a **fusion** **protein** comprising a zipper domain and a heterologous mammalian protein. In one embodiment, the heterologous mammalian protein comprises an extracellular domain. . . 358:26, 1992; Goodwin et al., Cell 73:447; 1993), which includes CD40 Ligand (CD40-L), CD27 Ligand (CD27-L), OX40 Ligand (OX40-L), and **TNF**. Structural studies of certain members of this family of proteins indicate that they form homotrimers. The inventive method will also. . .

DETDESC:

DETD(4)

In another embodiment, the heterologous mammalian protein comprises a soluble protein such as a cytokine; the resulting **fusion** **protein** forms an oligomer. Cytokines are soluble mediators released by cells during an immune or inflammatory response, which provide antigenically non-specific, intracellular signals that are crucial in regulating physiological processes. **TNF** .alpha., **TNF** .beta. and certain neurotrophins such as nerve growth factor (NGF) belong to the **TNF**/NGF family. Modeling studies of certain members of this family indicate that they are likely to form oligomers (Goh and Porter,. . .
DETDESC:

DETD(53)

This example describes construction of a CD40-L DNA construct to express a soluble CD40-L **fusion** **protein** referred to as trimeric CD40-L. CD40-L is a type II transmembrane protein found on activated T cells, that acts as. . . now abandoned, the disclosure of which is incorporated by reference herein. CD40-L is a member of the Tumor Necrosis Factor (**TNF**) family of proteins; several members of this family are believed to exist in trimeric form.

US PAT NO: 5,721,121 [IMAGE AVAILABLE] L7: 6 of 47
ABSTRACT:
The present invention relates to novel process for the preparation of glycoproteins by mammalian cell culture wherein the sialic acid content of the glycoprotein produced is controlled over a broad range of values by manipulating the cell culture environment. The invention provides for processes in which the sialic acid content of the glycoprotein is modified by changes in cell culture parameters which affect cell specific productivity. Preferred embodiments of the invention include cell culture processes in the osmolality of the cell culture is controlled as well as the concentration of a transcription enhancer during the production phase of the cell culture. The invention further provides for novel preparations of soluble type 1 tumor necrosis factor immunoglobulin G1 and their uses in the treatment of inflammatory or immune related disorders.

DETDESC:

DETD(127)

An . . . biological binding assay (ELIBA) was used to quantitate TNFR1-IgG.sub.1 in rat plasma. This assay is based on the ability of **TNF**-alpha coupled to horseradish peroxidase (**TNF**-alpha-HRP) to bind to the receptor portion of the TNFR1-IgG.sub.1 **fusion** **protein**. In this assay, Fab fragments of goat antihuman IgGFc coated on wells of microtiter plates were used to capture TNFR1-IgG.sub.1 by interaction with the Fc portion of the molecule. **TNF**-alpha-HRP was added to the wells and allowed to bind to the receptor portion of the captured TNFR1-IgG.sub.1. Quantification was determined. . .

US PAT NO: 5,741,774 [IMAGE AVAILABLE] L7: 2 of 47
ABSTRACT:
The present invention relates to the use of a cytokine regulatory agent to reduce the severity of rheumatoid arthritis.

SUMMARY:

BSUM(12)

In . . . if the levels of cytokines that contribute to the deleterious effects associated with rheumatoid arthritis could be regulated. For example, **TNF** is believed to have a role in rheumatoid arthritis and administration of a soluble **TNF** receptor fused to an immunoglobulin Fc domain resulted delayed the onset of an experimentally induced arthritis and resulted in a less severe grade of arthritis in mice. This result suggests that such a **fusion** **protein** could be useful for reducing the severity of rheumatoid arthritis.

SUMMARY:

BSUM(13)

Unfortunately, a biological material such as a **TNF** receptor/Fc domain **fusion** **protein** can be expensive to prepare in a form that is sufficiently pure for use as a therapeutic agent. In addition, such a **fusion** **protein** can present "foreign" epitopes that may induce an undesirable immune response in the treated subject. Such an immune response can decrease the effective concentration of the agent in the treated subject by binding to the **fusion** **protein** and can be involved in the formation of immune complexes, which can have deleterious effects in the treated subject. Thus,. . .

US PAT NO: 5,744,304 [IMAGE AVAILABLE] L7: 1 of 47
ABSTRACT:
The present invention describes methods of controlling and regulating the inflammatory reaction generated in response to various toxins, immunogens, pathogens and autoimmune insults. The method employs a vector that includes an anti-cytokine protein or antibacterial protein gene under the control of a cytokine responsive promoter. In animal models, adenoviral vectors successfully delivered the vectors to hepatic cells and were subsequently shown to respond only to stimulation by induced cytokines.

SUMMARY:

BSUM(8)

Other . . . have utilized gene therapy methods. For example, using gene transfer vectors in mice (Kolls et al., 1994), researchers constructed a **chimeric** **protein** capable of binding and neutralizing tumor necrosis factor (**TNF**). While the desired effect of producing high levels of constitutively produced **lymphotoxin** was achieved using this system, it was also reported that the animals were rendered highly susceptible to infection by Listeria. . .
DETDESC:

DETD(112)

Gene . . . non-replicating adenovirus (6.times.10.sup.12 plaque-forming units) or a DNA-liposome complex (10 mg DNA). The encoded antidote protein may be any of **TNF**-receptor-human immunoglobulin **fusion** **protein**, IL-10, fibrinogen, ACTH, or BPI. To provide multiple recombinant antidote proteins in vivo, more than one kind of vector-antidote protein. . .

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US PAT NO: 5,744,304 [IMAGE AVAILABLE] L7: 1 of 47 TITLE: Inflammation-induced expression of a recombinant gene
=> d his

(FILE 'USPAT' ENTERED AT 15:27:34 ON 01 MAY 1998)
L1 82 S (IMMUNOGLOBULIN OR IMMUNOGLOBIN OR IG)(W)FUSION L2 0 S L1(P)HCG
L3 2942 S FUSION PROTEIN
L4 308 S CHIMERIC PROTEIN
L5 3093 S L3 OR L4
L6 274 S L5 AND (TNF OR CACHECTIN OR LYMPHOTOXIN) L7 47 S L5(P)(TNF OR CACHECTIN OR LYMPHOTOXIN)

=> s (glycoprotein hormone) and (lh or hcg or fsh or tsh)

5500 GLYCOPROTEIN
12970 HORMONE
95 GLYCOPROTEIN HORMONE
(GLYCOPROTEIN(W)HORMONE)
6174 LH
1358 HCG
1004 FSH
881 TSH
L8 57 (GLYCOPROTEIN HORMONE) AND (LH OR HCG OR FSH OR TSH)
=> s l5 and l8

L9 7 L5 AND L8

=> d 1-7

1. 5,744,448, Apr. 28, 1998, Human follicle stimulating hormone receptor; Christie Ann Kelton, et al., 514/12; 424/158.1; 514/841, 843; 530/350 [IMAGE AVAILABLE]

2. 5,736,135, Apr. 7, 1998, Method for making variant secreted proteins with altered properties; David V. Goeddel, et al., 424/94.64, 94.63; 435/212, 226, 252.3; 536/23.2 [IMAGE AVAILABLE]

3. 5,705,478, Jan. 6, 1998, Covalently linked .beta. subunits of the glycoprotein hormones as antagonists; Irving Boime, 514/8, 2; 530/397, 398, 399 [IMAGE AVAILABLE]

4. 5,688,666, Nov. 18, 1997, Growth hormone variants with altered binding properties; Steven H. Bass, et al., 435/69.4; 530/399 [IMAGE AVAILABLE]

5. 5,686,597, Nov. 11, 1997, Thrombin receptor homolog; Roger Coleman, et al., 536/23.5; 435/2, 7.21, 69.1, 252.3, 254.11 [IMAGE AVAILABLE]
6. 5,607,691, Mar. 4, 1997, Compositions and methods for enhanced drug delivery; Ron L. Hale, et al., 424/449; 514/1, 2, 26, 169, 183, 553, 556; 604/20 [IMAGE AVAILABLE]

7. 5,223,408, Jun. 29, 1993, Method for making variant secreted proteins with altered properties; David V. Goeddel, et al., 435/69.3, 69.4, 69.52, 69.6, 69.7, 172.3, 189, 195, 215, 216, 226 [IMAGE AVAILABLE]
=> d ab 6

US PAT NO: 5,607,691 [IMAGE AVAILABLE] L9: 6 of 7
ABSTRACT:
The present invention relates to methods of delivering pharmaceutical agents across membranes, including the skin layer or mucosal membranes of a patient. A pharmaceutical agent is covalently bonded to a chemical modifier, via a physiologically cleavable bond, such that the membrane transport and delivery of the agent is enhanced.

=> s dimerizing fragment

799 DIMERIZING
31986 FRAGMENT
L10 0 DIMERIZING FRAGMENT

(DIMERIZING(W)FRAGMENT)

=> s dimerizing

L11 799 DIMERIZING

=> s l11(p)(chimer? or fusion()protien)

3191 CHIMER?
39921 FUSION
55 PROTIEN
L12 2 L11(P)(CHIMER? OR FUSION(W)PROTIEN)

=> d 1,2

1. 5,219,739, Jun. 15, 1993, DNA sequences encoding bVEGF120 and hVEGF121 and methods for the production of bovine and human vascular endothelial cell growth factors, bVEGF.sub.120 and hVEGF.sub.121; Edmund G. Tischer, et al., 435/69.4, 69.1, 320.1; 530/399; 536/23.5, 23.51 [IMAGE AVAILABLE]

2. 5,194,596, Mar. 16, 1993, Production of vascular endothelial cell growth factor; Edmund G. Tischer, et al., 530/399, 350 [IMAGE AVAILABLE]
=> d kwic

US PAT NO: 5,219,739 [IMAGE AVAILABLE] L12: 1 of 2
DETDESC:

DETD(29)

In order to prepare the **chimeric** growth factors of the invention, a DNA sequence encoding each desired chain is inserted into a suitable expression vector, e.g.. . . (1989) 161(2):851-858. If the correct dimer structure is not obtained by this route, or if the two chains of the **chimera** are synthesized in different hosts, then an example of one means of refolding and **dimerizing** the chains would be to treat the partially-purified or purified chains with guanidine-HCl, Na.sub.2 SO.sub.3 and Na.sub.2 S.sub.4 O.sub.6, as. . .

=> d kwic 2

US PAT NO: 5,194,596 [IMAGE AVAILABLE] L12: 2 of 2
DETDESC:

DETD(27)

In order to prepare the **chimeric** growth factors of the invention, a DNA sequence encoding each desired chain is inserted into a suitable expression vector, e.g.. . . (1989) 61(2):851-858. If the correct dimer structure is not obtained by this route, or if the two chains of the **chimera** are synthesized in different hosts, then an example of one means of refolding and **dimerizing** the chains would be to treat the partially-purified or purified chains with guanidine-HCl, Na.sub.2 SO.sub.3 and Na.sub.2 S.sub.4 O.sub.6, as. . .

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/H = Help /L = Logoff /NOMENU = Command Mode
Enter an option number to view information or to connect to an online service. Enter a BEGIN command plus a file number to search a database (e.g., B1 for ERIC).
? b 410

01may98 14:44:24 User217743 Session D445.1
$0.00 0.003 Hrs FileHomeBase
$0.00 Estimated cost FileHomeBase
$0.00 Estimated cost this search
$0.00 Estimated total session cost 0.003 Hrs.

File 410:Chronolog(R) 1981-1998/May
(c) 1998 The Dialog Corporation plc

Set Items Description
--- ----- ---------
? set hi %%%;set hi %%%

HILIGHT set on as '%%%'%%%
%%%HILIGHT set on as '%%%'
? b 411

01may98 14:44:36 User217743 Session D445.2
$0.00 0.003 Hrs File410
$0.00 Estimated cost File410
$0.00 Estimated cost this search
$0.00 Estimated total session cost 0.006 Hrs.
File 411:DIALINDEX(R)

DIALINDEX(R)
(c) 1998 The Dialog Corporation plc

*** DIALINDEX search results display in an abbreviated *** *** format unless you enter the SET DETAIL ON command. *** ?
set files biochem

>>> 162 is unauthorized
>>> 352 is unauthorized
>>>2 of the specified files are not available
You have 32 files in your file list.
(To see banners, use SHOW FILES command)
? s hybrid()protein()dimer

Your SELECT statement is:
s hybrid()protein()dimer

Items File
----- ----
<------User Break------>
u!
? s (hybrid()protein() or chimeric or fusion)()dimer

Your SELECT statement is:
s (hybrid()protein() or chimeric or fusion)()dimer

Items File
----- ----
>>>Operator "OR" in invalid position
? s (hybrid()protein or chimeric or fusion)()dimer

Your SELECT statement is:
s (hybrid()protein or chimeric or fusion)()dimer

Items File
----- ----
7 5: BIOSIS PREVIEWS(R)_1969-1998/Apr W4
2 156: Toxline(R)_1965-1998/Feb
2 348: EUROPEAN PATENTS_1978-1998/Apr W17
2 357: Derwent Biotechnology Abs_1982-1998/May B2
3 399: CA SEARCH(R)_1967-1998/UD=12818
1 434: Scisearch(R) Cited Ref Sci_1974-1998/Apr W3
6 files have one or more items; file list includes 32 files.
? rf

Your last SELECT statement was:
S (HYBRID()PROTEIN OR CHIMERIC OR FUSION)()DIMER

Ref Items File
--- ----- ----
N1 7 5: BIOSIS PREVIEWS(R)_1969-1998/Apr W4
N2 3 399: CA SEARCH(R)_1967-1998/UD=12818
N3 2 156: Toxline(R)_1965-1998/Feb
N4 2 348: EUROPEAN PATENTS_1978-1998/Apr W17
N5 2 357: Derwent Biotechnology Abs_1982-1998/May B2
N6 1 434: Scisearch(R) Cited Ref Sci_1974-1998/Apr W3
N7 0 40: Enviroline(R)_1975-1998/Mar
N8 0 41: Pollution Abs_1970-1998/Apr
N9 0 68: Env.Bib._1974-1998/Mar
N10 0 71: ELSEVIER BIOBASE_1994-1998/Apr W3
6 files have one or more items; file list includes 32 files.
- Enter P or PAGE for more -
? b n1-n6

01may98 14:47:35 User217743 Session D445.3
$1.50 0.050 Hrs File411
$1.50 Estimated cost File411
$1.50 Estimated cost this search
$1.50 Estimated total session cost 0.056 Hrs.

SYSTEM:OS - DIALOG OneSearch
File 5:BIOSIS PREVIEWS(R) 1969-1998/Apr W4
(c) 1998 BIOSIS
File 399:CA SEARCH(R) 1967-1998/UD=12818
(c) 1998 American Chemical Society
*File 399: Use is subject to the terms of your user/customer agreement. RANK charge added; see HELP RATES 399.
File 156:Toxline(R) 1965-1998/Feb
(c) format only 1998 The Dialog Corporation
File 348:EUROPEAN PATENTS 1978-1998/Apr W17
(c) 1998 EUROPEAN PATENT OFFICE
*File 348: *** All EPO Fulltext data is now online and current! *** New fulltext will be added weekly. See HELP NEWS 348 for details. File 357:Derwent Biotechnology Abs 1982-1998/May B2
(c) 1998 Derwent Publ Ltd
File 434:Scisearch(R) Cited Ref Sci 1974-1998/Apr W3
(c) 1998 Inst for Sci Info

Set Items Description
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? s (hybrid()protein or chimeric or fusion)()dimer

159823 HYBRID
2695994 PROTEIN
2593 HYBRID(W)PROTEIN
38452 CHIMERIC
270152 FUSION
81897 DIMER
S1 17 (HYBRID()PROTEIN OR CHIMERIC OR FUSION)()DIMER ? rd

>>>Duplicate detection is not supported for File 348.

>>>Records from unsupported files will be retained in the RD set. ...completed examining records
S2 14 RD (unique items)
? t s2/3,ab/all

>>>No matching display code(s) found in file(s): 399

2/3,AB/1 (Item 1 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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14095349 BIOSIS Number: 01095349
Molecular genetic study of the interaction of Sindbis virus E2 with Ross River virus E1 for virus budding
Yao J; Strauss E G; Strauss J H
Div. Biol. 15629, California Inst. Technol., Pasadena, CA 91125, USA Journal of Virology 72 (2). 1998. 1418-1423.
Full Journal Title: Journal of Virology
ISSN: 0022-538X
Language: ENGLISH
Print Number: Biological Abstracts Vol. 105 Iss. 005 Ref. 067624 Glycoprotein PE2 of Sindbis virus will form a heterodimer with glycoprotein E1 of Ross River virus that is cleaved to an E2/E1 heterodimer and transported to the cell plasma membrane, but this %%%chimeric%%% %%%heterodimer%%% fails to interact with Sindbis virus nucleocapsids, and very little budding to produce mature virus occurs upon infection with chimeric viruses. We have isolated in both Sindbis virus E2 and in Ross River virus E1 a series of suppressing mutations that adapt these two proteins to one another and allow increased levels of chimeric virus production. Two adaptive E1 changes in an ectodomain immediately adjacent to the membrane anchor and five adaptive E2 changes in a 12-residue ectodomain centered on Asp-242 have been identified. One change in Ross River virus E1 (Gln-411 fwdarw Leu) and one change in Sindbis virus E2 (Asp-248 fwdarw Tyr) were investigated in detail. Each change individually leads to about a 10-fold increase in virus production, and combined the two changes lead to a 100-fold increase in virus. During passage of a chimeric virus containing Ross River virus E1 and Sindbis virus E2, the E2 change was first selected, followed by the E1 change. Heterodimers containing these two adaptive mutations have a demonstrably increased degree of interaction with Sindbis virus nucleocapsids. In the parental chimera, no interaction between heterodimers and capsids was visible at the plasma membrane in electron microscopic studies, whereas alignment of nucleocapsids along the plasma membrane, indicating interaction of heterodimers with nucleocapsids, was readily seen in the adapted chimera. The significance of these findings in light of our current understanding of alphavirus budding is discussed.

2/3,AB/2 (Item 2 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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13781813 BIOSIS Number: 99781813
Synthesis of green fluorescent protein-ricin and monitoring of its intracellular trafficking
Tagge E; Harris B; Burbage C; Hall P; Vesely J; Willingham M; Frankel A Hollings Cancer Cent., Room 311, 86 Jonathan Lucas St., Charleston, SC 29425, USA
Bioconjugate Chemistry 8 (5). 1997. 743-750.
Full Journal Title: Bioconjugate Chemistry
ISSN: 1043-1802
Language: ENGLISH
Print Number: Biological Abstracts Vol. 104 Iss. 010 Ref. 139417 We performed genetic engineering to fuse enhanced green fluorescent protein (EGFP) to the N terminus of RTA, expressed the fusion protein in Escherichia coli, purified and reassociated EGFP-RTA with plant RTB, and purified EGFP-ricin by size exclusion HPLC. The %%%fusion%%% %%%heterodimer%%% was able to bind galactosides, intoxicate cells, and show strong fluorescence. Mammalian cells incubated with EGFP-ricin showed strong cell surface fluorescence at 4 degree C and, on incubation at 37 degree C, distributed initially to endosomes and then to Golgi vesicles. Variable sensitivity of mammalian cells to ricin and ricin fusion proteins may be due in part to different patterns of intracellular routing. Cells were incubated with ricin or EGFP-ricin, and inhibition of protein synthesis was measured. Human hepatocellular carcinoma Hep3B cells were 10-fold more sensitive to ricin and 85-fold more sensitive to EGFP-ricin than human epidermoid carcinoma KB cells. Epifluorescence microscopy of cells incubated with EGFP-ricin showed greater localization of the fluorescence signal in the Golgi compartments in Hep3B cells than in KB cells. These data support a model requiring a Golgi-dependent step in cell intoxication by ricin. The work further identifies the usefulness of green fluorescent protein fusions in the study of retrograde transport of internalized peptides.

2/3,AB/3 (Item 3 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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13404844 BIOSIS Number: 99404844
The leucine zipper domain controls the orientation of AP-1 in the NFAT cntdot AP-1 cntdot DNA complex
Erlanson D A; Chytil M; Verdine G L
Dep. Chem. Chem. Biol., Harvard Univ., Cambridge, MA 02138, USA Chemistry & Biology (London) 3 (12). 1996. 981-991.
Full Journal Title: Chemistry & Biology (London)
ISSN: 1074-5521
Language: ENGLISH
Print Number: Biological Abstracts Vol. 103 Iss. 006 Ref. 076987 Background: Heterologous transcription factors bound to adjacent sites in eukaryotic promoters often exhibit cooperative behavior. In most instances, the molecular basis for this cooperativity is poorly understood. Our efforts have been directed toward elucidation of the mechanism of cooperativity between NFAT and AP-1, two proteins that coordinately direct expression of the T-cell growth factor interleukin-2 (IL-2). Results: We have previously shown that NFAT1 orients the two subunits of AP-1, c-Jun and c-Fos, on DNA through direct protein sbd protein interactions. In the present study, we have constructed cJun sbd cFos chimeric proteins and determined their orientation using a novel affinity-cleavage technology based on chemical ligation. We find that, in the presence of NFAT, the %%%chimeric%%% %%%heterodimer%%% binds in such a way as to preserve

the orientation of the AP-1 leucine zipper, but not that of the basic region. Conclusions: Protein-protein interactions between NFAT and the leucine zipper of AP-1 enable the two proteins to bind DNA cooperatively and coordinately regulate the IL-2 promoter. The chemical ligation technology presented here provides a powerful strategy for affinity cleavage studies, including those using recombinant proteins.

2/3,AB/4 (Item 4 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1998 BIOSIS. All rts. reserv.

11517100 BIOSIS Number: 98117100
Modulation of cell adhesion by changes in alpha-L beta-2 (LFA-1, CD11a-CD18) cytoplasmic domain-cytoskeleton interaction
Peter K; O'Toole T E
Innere Med. III, Univ. Heidelberg, Bergheimerstr. 58, 69115 Heidelberg, Germany
Journal of Experimental Medicine 181 (1). 1995. 315-326.
Full Journal Title: Journal of Experimental Medicine
ISSN: 0022-1007
Language: ENGLISH
Print Number: Biological Abstracts Vol. 099 Iss. 006 Ref. 073657 The integrin alpha-L beta-2 (leukocyte function-associated molecule 1, CD11a/CD18) mediates activation-dependent adhesion of leukocytes. The cytoplasmic domains of alpha-L beta-2 have been demonstrated to modulate adhesiveness of alpha-L beta-2. Affinity changes of alpha-L beta-2 for its ligand or postreceptor events can be responsible for this modulation of adhesiveness. To investigate the possible role of the alpha-L beta-2. cytoplasmic domains in postreceptor events we constructed cDNA encoding chimeric proteins with intracellular alpha-L beta-2 domains, which are responsible for alpha-L beta-2 specific intracellular interactions, and extracellular alpha-IIb beta-3 (GP IIb/IIIa) domains, which allow the assessment of the receptor affinity state. The cDNA was stably transfected in Chinese hamster ovary cells and %%%chimeric%%% %%%heterodimer%%% formation proven by immunoprecipitations and flow cytometry. The chimeric receptors mediate adhesion to immobilized fibrinogen, and this adhesion is increased by phorbol myristate acetate and abolished by cytochalasin D. However, neither treatment affects the affinity state of the chimeric receptor, suggesting involvement of the cytoskeleton in the regulation of alpha-L beta-2 mediated cell adhesion. To exclude the possibility of postoccupancy affinity changes of the chimeric receptors, we locked the receptors into a high affinity state by creating a deletion variant. The region deleted (VGFFK) is highly conserved in integrin alpha subunit cytoplasmic domains. Cotransfection of this deletion variant with a beta subunit truncation (beta-3 DELTA-274) and a triple mutation at 758-760 (TTT to AAA) of beta-2 abolishes adhesion without changing the affinity state. A single mutation (TTT to TAT) reduces adhesion by half without affinity change. Scanning electron microscopy reveals impaired spreading of these truncated/mutated chimeras. Immunofluorescence microscopy demonstrates a correlation between impaired adhesion and a decrease in the ability to form focal adhesions and to organize the cytoskeleton into stress fibers. These results describe the integrin/cytoskeleton interaction, the organization of the cytoskeleton, and cell spreading as postreceptor events modulating alpha-L beta-2 cytoplasmic domain mediated cell adhesion. Furthermore, we demonstrate that the cytoplasmic domain of the beta-2 subunit, and within it the TTT region, are required for these postreceptor events. Additionally, we present a new approach, using deletion variants to lock integrins in a high affinity state without interfering with the investigated integrin/cytoskeleton interaction. This approach may be generally useful to investigate the role of postreceptor events in integrin-mediated cell adhesion and migration.

2/3,AB/5 (Item 5 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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11444145 BIOSIS Number: 98044145
A general method for facilitating heterodimeric pairing between two proteins: Application to expression of alpha and beta T-cell receptor extracellular segments
Chang H-C; Bao Z-Z; Yao Y; Tse A G D; Goyarts E C; Madsen M; Kawasaki E; Brauer P P; Sacchettini J C; Nathenson S G; Reinherz E L
Lab. Immunobiology, Dana-Farber Cancer Inst., Harvard Med. Sch., Boston, MA 02115, USA
Proceedings of the National Academy of Sciences of the United States of America 91 (24). 1994. 11408-11412.
Full Journal Title: Proceedings of the National Academy of Sciences of the United States of America
ISSN: 0027-8424
Language: ENGLISH
Print Number: Biological Abstracts Vol. 099 Iss. 003 Ref. 028689 Generation of soluble T-cell receptor (TCR) molecules by a variety of genetic engineering methods has been hampered by inefficient pairing of alpha and beta subunits in the absence of their respective transmembrane regions and associated CD3 components. To overcome this obstacle, we have added 30-amino acid-long segments to the carboxyl termini of alpha and beta extracellular domains via a cleavable flexible linker. These peptide segments (BASE-p1 for alpha and ACID-p1 for beta) have been previously shown to selectively associate to form a stable heterodimeric coiled coil termed a leucine zipper. Homodimeric structures are not permitted due to electrostatic repulsion among amino acid side chains. Expression of a representative TCR-leucine zipper fusion protein in a baculovirus expression system results in production of alpha-beta TCR heterodimer at 0.6-1.4 mg/liter. This yield is 5- to 10-fold greater than that of the TCR expressed in the absence of the synthetic leucine zipper sequence. The structure of the TCR component of the %%%fusion%%% %%%heterodimer%%% was judged to be native when probed with a panel of 17 mAbs specific for a and B constant and variable domains. A mAb specific for the isolated BASE-p1/ACID-p1 coiled coil was also generated and shown to react with the TCR fusion protein. The above technology should be broadly useful in the efficient production and purification of TCRs as well as other heterodimeric proteins.

2/3,AB/6 (Item 6 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1998 BIOSIS. All rts. reserv.

10131310 BIOSIS Number: 95131310
SOLUBLE TUMOR NECROSIS FACTOR RECEPTOR INHIBITION OF HUMAN IMMUNODEFICIENCY VIRUS ACTIVATION
HOWARD O M Z; CLOUSE K A; SMITH C; GOODWIN R G; FARRAR W L LAB. MOL. IMMUNOREGULATION, BIOL. RES. MODIFIERS PROGRAM, NATIONAL CANCER INST.-FREDERICK CANCER RES. DEVELOPMENT CENTER, PO BOX B, FREDERICK, MD 21702, USA.
PROC NATL ACAD SCI U S A 90 (6). 1993. 2335-2339.

CODEN: PNASA Full Journal Title: Proceedings of the National Academy of Sciences of the United States of America
Language: ENGLISH
The inflammatory cytokine tumor necrosis factor .alpha. (TNF-.alpha.) has been shown to stimulate human immunodeficiency virus type 1 (HIV-1) replication in both chronically and acutely infected T lymphocytes and monocytes. Transcriptional activation of the HIV long terminal repeat and subsequent increase in virus production are linked to TNF activation of the cellular transcription factor NF-.kappa.B. Here we report the use of two forms of soluble recombinant type 1 (p80) TNF receptor to inhibit TNF-induced HIV activation in vitro. One receptor form is a monomer containing the entire 236 residues of the extracellular (ligand-binding) portion of p80. A second receptor form is a %%%chimeric%%% %%%homodimer%%% containing these residues fused to a truncated human IgG1 immunoglobulin heavy chain and, thus, resembles a bivalent antibody without light chains. These recombinant receptor proteins were tested for their ability to inhibit TNF-.alpha.-induced expression of HIV-1 in chronically infected human cell lines. We also examined the ability of the soluble receptors to limit the activation of the HIV-long terminal repeat transcription. The soluble TNF receptor dimer was most effective at blocking TNF-.alpha.-induced HIV-1 expression in both monocytoid and lymphoid cells. The molar ratio of TNF-receptor dimer to TNF-.alpha. found to be most effective was, at least, 5:1. We conclude that at specific TNF/soluble TNF-receptor dimer ratios, TNF-.alpha.-induced HIV-1 transcription and expression can be limited in vitro.

2/3,AB/7 (Item 7 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1998 BIOSIS. All rts. reserv.

7316687 BIOSIS Number: 38097208
RECOMBINANT DHFR %%%FUSION%%% %%%DIMER%%%
IWAKURA M; MATTHEWS C R
DEP. CHEM., PA. STATE UNIV., UNIVERSITY PARK, PA. 16802. THIRTY-FOURTH ANNUAL MEETING OF THE BIOPHYSICAL SOCIETY, BALTIMORE, MARYLAND, USA, FEBRUARY 18-22, 1990. BIOPHYS J 57 (2 PART 2). 1990. 436A. CODEN: BIOJA
Language: ENGLISH
Document Type: CONFERENCE PAPER

2/3,AB/8 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
(c) 1998 American Chemical Society. All rts. reserv.

122127577 CA: 122(11)127577m PATENT
Biologically active polypeptide fusion dimers.
INVENTOR(AUTHOR): Thomason, Arlen R.
LOCATION: USA
ASSIGNEE: Amgen Inc.
PATENT: European Pat. Appl. ; EP 618227 A1 DATE: 941005 APPLICATION: EP 94105075 (940331) *US 41635 (930401)
PAGES: 30 pp. CODEN: EPXXDW LANGUAGE: English CLASS: C07K-015/00A; C07K-013/00B; C12N-015/12B; C12N-015/18B; A61K-037/36B
DESIGNATED COUNTRIES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE

2/3,AB/9 (Item 2 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
(c) 1998 American Chemical Society. All rts. reserv.

121173277 CA: 121(15)173277r JOURNAL
Properties of permease dimer, a fusion protein containing two lactose permease molecules from Escherchia coli
AUTHOR(S): Sahin-Toth, Miklos; Lawrence, Mary C.; Kaback, H. Ronald LOCATION: Howard Hughes Med. Inst., Univ. California, Los Angeles, CA, 90024-1662, USA
JOURNAL: Proc. Natl. Acad. Sci. U. S. A. DATE: 1994 VOLUME: 91 NUMBER: 12 PAGES: 5421-5 CODEN: PNASA6 ISSN: 0027-8424 LANGUAGE: English

2/3,AB/10 (Item 3 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
(c) 1998 American Chemical Society. All rts. reserv.

121033159 CA: 121(3)33159d PATENT
A subpopulation of Mac-1 (CD11b/CD18) molecules which mediate neutrophil adhesion to ICAM-1 and fibrinogen and its monoclonal antibodies INVENTOR(AUTHOR): Diamond, Michael; Springer, Timothy A. LOCATION: USA
ASSIGNEE: Center for Blood Research
PATENT: PCT International ; WO 9408620 A1 DATE: 940428
APPLICATION: WO 93US9777 (931012) *US 958904 (921009) *US 964156 (921022) PAGES: 119 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: A61K-039/395A; C07K-015/28B DESIGNATED COUNTRIES: AU; CA; JP; KR DESIGNATED REGIONAL: AT ; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE

2/3,AB/11 (Item 1 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS
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00636901
ORDER fax of complete patent from Dialog SourceOne. See HELP ORDER 348 Biologically active polypeptide fusion dimers.
Biologisch aktive Polypeptid Fusionsdimere.
Dimeres de fusionspolypeptidiques biologiquement actifs.
PATENT ASSIGNEE:
AMGEN INC., (923233), Amgen Center, 1840 Dehavilland Drive, Thousand Oaks, CA 91320-1789, (US), (applicant designated states: AT;BE;CH;DE;DK;ES;FR;GB;GR;IE;IT;LI;LU;MC;NL;PT;SE)
INVENTOR:
Thomason, Arlen R., 2298 Watertown Court, Thousand Oaks, CA 91360, (US) LEGAL REPRESENTATIVE:
Vossius, Volker, Dr. et al (12524), Dr. Volker Vossius Patentanwaltskanzlei - Rechtsanwaltskanzlei Holbeinstrasse 5, D-81679 Munchen, (DE)
PATENT (CC, No, Kind, Date): EP 618227 A1 941005 (Basic) APPLICATION (CC, No, Date): EP 94105075 940331;
PRIORITY (CC, No, Date): US 41635 930401
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
INTERNATIONAL PATENT CLASS: C07K-015/00; C07K-013/00; C12N-015/12; C12N-015/18; A61K-037/36;

ABSTRACT EP 618227 A1
The present invention provides a biologically active multimeric polypeptide molecule in which two or more monomeric subunits are linked together as a single polypeptide ("fusion multimer"). These fusion multimers are

more easily and rapidly refolded than unfused multimers, because the reactions necessary to generate the biologically active multimeric form of the polypeptide proceed with first order, rather than second or higher order, reaction kinetics. Fusion multimers also eliminate the simultaneous formation of undesired polypeptide by-products during refolding. The fusion multimers of the present invention specifically include PDGF fusion dimers.
ABSTRACT WORD COUNT: 91

LANGUAGE (Publication,Procedural,Application): English; English; English FULLTEXT AVAILABILITY:
Available Text Language Update Word Count
CLAIMS A (English) EPABF2 501
SPEC A (English) EPABF2 8793
Total word count - document A 9294
Total word count - document B 0
Total word count - documents A + B 9294

2/3,AB/12 (Item 2 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS
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00450411
ORDER fax of complete patent from Dialog SourceOne. See HELP ORDER 348 PRODUCTION OF VASCULAR ENDOTHELIAL CELL GROWTH FACTOR
HERSTELLUNG DES VASKULAREN ENDOTHELIALEN ZELLWACHSTUMSFAKTORS PRODUCTION DE FACTEUR DE CROISSANCE DE CELLULES ENDOTHELIALES VASCULAIRES PATENT ASSIGNEE:
SCIOS NOVA INC., (1619850), 2450 Bayshore Parkway, Mountain View, CA 94043, (US), (applicant designated states:
AT;BE;CH;DE;DK;ES;FR;GB;IT;LI;LU;NL;SE)
INVENTOR:
TISCHER, Edmund, G., 3316 Kenneth Drive, Palo Alto, CA 94303, (US) ABRAHAM, Judith, A., 655 S. Fairoaks Avenue, 1-207, Sunnyvale, CA 94086, (US)
FIDDES, John, C., 2320 Bryant Street, Palo Alto, CA 94301, (US) MITCHELL, Richard, L., 15920, 177th Avenue NE, Woodinville Washington 98072, (US)
LEGAL REPRESENTATIVE:
Goldin, Douglas Michael et al (31061), J.A. KEMP & CO. 14, South Square Gray's Inn, London WC1R 5LX, (GB)
PATENT (CC, No, Kind, Date): EP 484401 A1 920513 (Basic)
EP 484401 A1 920819
EP 484401 B1 960911
WO 9102058 910221
APPLICATION (CC, No, Date): EP 90911525 900727; WO 90US4227 900727 PRIORITY (CC, No, Date): US 387545 890727; US 450883 891214 DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; IT; LI; LU; NL; SE
INTERNATIONAL PATENT CLASS: C12N-015/12; C12N-015/18; C12N-005/10; A61K-038/27;
LANGUAGE (Publication,Procedural,Application): English; English; English FULLTEXT AVAILABILITY:
Available Text Language Update Word Count
CLAIMS B (English) EPAB96 1760
CLAIMS B (German) EPAB96 1678
CLAIMS B (French) EPAB96 1929
SPEC B (English) EPAB96 23518
Total word count - document A 0
Total word count - document B 28885
Total word count - documents A + B 28885

2/3,AB/13 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs
(c) 1998 Derwent Publ Ltd. All rts. reserv.

172040 DBA Accession No.: 94-14591 PATENT
Multimeric fusion protein production - human single chain platelet-derived growth factor-B or -A, vascular endothelial cell growth factor, placental growth factor or platelet-derived growth factor-inhibitor gene cloning
PATENT ASSIGNEE: Amgen 1994
PATENT NUMBER: EP 618227 PATENT DATE: 941005
WPI ACCESSION NO.: 94-304405 (9438)
PRIORITY APPLIC. NO.: US 41635 APPLIC. DATE: 930401
NATIONAL APPLIC. NO.: EP 94105075 APPLIC. DATE: 940331
LANGUAGE: English
ABSTRACT: A new protein comprises 2 or more polypeptide subunits of a naturally occurring multimer, incorporated head-to-tail in a single continuous polypeptide. The protein is preferably a single chain platelet-derived growth factor (PDGF) family multimer. PDGF-A, PDGF-B, vascular endothelial cell growth factor or placental growth factor sequences may be used, especially a 109-amino-acid and/or a 119-amino-acid cleavage product of human PDGF-B. A PDGF-BB %%%fusion%%% %%%dimer%%% is claimed. The fusion protein may be expressed in a transfected host cell. A fusion protein as above with PDGF-inhibitor activity has at least 1 biologically inactive subunit and 1 active subunit. The fusion multimers are more easily and rapidly refolded than unfused multimers, since the reactions necessary to generate the biologically active multimeric form proceed with 1st-order rather than 2nd-order kinetics. In addition, simultaneous formation of undesired byproducts during refolding is avoided. The subunits may be linked directly or via a spacer. (30pp)

2/3,AB/14 (Item 2 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs
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120050 DBA Accession No.: 91-07692
Isolation of active homodimers of HIV-1 reverse-transcriptase by the application of a genetically engineered metal binding peptide - HIV virus-1 reverse-transcriptase with metal binding affinity tail; enzyme purification from Escherichia coli by metal chelate affinity chromatography (conference abstract)
AUTHOR: Chattopadhyay D; Evans D B; Deibel Jr M R; Einspahr H M; Sharma S K
CORPORATE AFFILIATE: Upjohn
CORPORATE SOURCE: Upjohn Laboratories, Kalamazoo, Michigan 49001, USA. JOURNAL: Abstr.Pap.Am.Chem.Soc. (201 Meet., Pt.1, BIOT4) 1991 CODEN: ACSRAL
LANGUAGE: English
ABSTRACT: A metal binding peptide was engineered onto the N-terminus of HIV virus-1 reverse-transcriptase (RT, EC-2.7.7.49) for specific and rapid isolation by metal chelate affinity chromatography (immobilized metal affinity chromatography). A recombinant fusion protein from a crude Escherichia coli extract was bound to an immobilized nickel column. Most of the contaminating E. coli proteins were eluted with 35 mM-100 mM imidazole, and the bound fusion protein was eluted with 300 mM imidazole. The peptide eluting later was in a form that migrated on SDS-PAGE predominantly as a 66 kDa polypeptide. HPLC was carried out in conjunction with assays of RT and RNA-ase-H activities to define the nature of the 66 kDa protein. Results indicated that the isolated 66 kDa HIV virus

RT can be resolved into active homodimers (70%) and (presumably) inactive monomers (30%). Preparation of a similar %%%chimeric%%% %%%heterodimer%%% (p66/p51) was presented. (0 ref) ? s leucine()zipper

```
      87334 LEUCINE
      10114 ZIPPER
   S3   8820 LEUCINE()ZIPPER
? s glycoprotein()hormone

     187148 GLYCOPROTEIN
     775094 HORMONE
   S4   2225 GLYCOPROTEIN()HORMONE
? s s4 and s3

       2225 S4
       8820 S3
   S5    20 S4 AND S3
? rd

>>>Duplicate detection is not supported for File 348.

>>>Records from unsupported files will be retained in the RD set. ...completed examining records
   S6    17 RD (unique items)
? s s6 not s2

         17 S6
         14 S2
   S7    17 S6 NOT S2
? ds

Set    Items  Description
S1       17  (HYBRID()PROTEIN OR CHIMERIC OR FUSION()DIMER S2       14  RD (unique items)
S3     8820  LEUCINE()ZIPPER
S4     2225  GLYCOPROTEIN()HORMONE
S5       20  S4 AND S3
S6       17  RD (unique items)
S7       17  S6 NOT S2
? t s7/6/all
```

7/6/1 (Item 1 from file: 5)
11619186 BIOSIS Number: 98219186
Upstream stimulatory factor, a basic-helix-loop-helix-zipper protein, regulates the activity of the alpha-%%%glycoprotein%%% %%%hormone%%% subunit gene in pituitary cells
Print Number: Biological Abstracts Vol. 099 Iss. 010 Ref. 141362

7/6/2 (Item 2 from file: 5)
10403549 BIOSIS Number: 96003549
MODIFICATION OF DNA TOPOISOMERASE II ACTIVITY VIA DIRECT INTERACTIONS WITH THE CYCLIC ADENOSINE-3' 5'-MONOPHOSPHATE RESPONSE ELEMENT-BINDING PROTEIN AND RELATED TRANSCRIPTION FACTORS

7/6/3 (Item 1 from file: 434)
15904748 Genuine Article#: BJ31P Number of References: 140 Title: The gonadotropin genes: Evolution of distinct mechanisms for hormonal control (ABSTRACT AVAILABLE)

7/6/4 (Item 2 from file: 434)
15391039 Genuine Article#: WD804 Number of References: 193 Title: Structural and functional diversity in the leucine rich repeat family of proteins

7/6/5 (Item 3 from file: 434)
11855529 Genuine Article#: JR313 Number of References: 63 Title: MUTUAL CROSS-INTERFERENCE BETWEEN GLUCOCORTICOID RECEPTOR AND CREB INHIBITS TRANSACTIVATION IN PLACENTAL CELLS

7/6/6 (Item 4 from file: 434)
11648171 Genuine Article#: HZ964 Number of References: 34 Title: ANALYSIS OF DNA-SEQUENCES REQUIRED FOR PITUITARY-SPECIFIC EXPRESSION OF THE %%%GLYCOPROTEIN%%% %%%HORMONE%%% ALPHA-SUBUNIT GENE (Abstract Available)

7/6/7 (Item 5 from file: 434)
11589134 Genuine Article#: HV306 Number of References: 43 Title: DEOXYRIBONUCLEASE-HYPERSENSITIVE SITES IN THE %%%GLYCOPROTEIN%%% %%%HORMONE%%% ALPHA-SUBUNIT GENE FROM TROPHOBLASTIC AND NONTROPHOBLASTIC HUMAN TUMOR-CELL LINES - CORRELATION WITH EXPRESSION AND EFFECT OF CHEMICAL INDUCERS (Abstract Available)

7/6/8 (Item 6 from file: 434)
11541835 Genuine Article#: HQ338 Number of References: 57 Title: TISSUE-SPECIFIC GENE-EXPRESSION IN THE PITUITARY - THE %%%GLYCOPROTEIN%%% %%%HORMONE%%% ALPHA-SUBUNIT GENE IS REGULATED BY A GONADOTROPE-SPECIFIC PROTEIN (Abstract Available)

7/6/9 (Item 7 from file: 434)
11158395 Genuine Article#: GL704 Number of References: 51 Title: THE GENE ENCODING OVINE FOLLICLE-STIMULATING HORMONE-BETA - ISOLATION, CHARACTERIZATION, AND COMPARISON TO A RELATED OVINE GENOMIC SEQUENCE (Abstract Available)

7/6/10 (Item 8 from file: 434)
11148013 Genuine Article#: GL389 Number of References: 42 Title: BINDING-SPECIFICITY OF CYCLIC ADENOSINE 3',5'-MONOPHOSPHATE-RESPONSIVE ELEMENT (CRE)-BINDING PROTEINS AND ACTIVATING TRANSCRIPTION FACTORS TO NATURALLY-OCCURRING CRE SEQUENCE VARIANTS (Abstract Available)

7/6/11 (Item 9 from file: 434)
11114683 Genuine Article#: GH333 Number of References: 59 Title: EXPRESSION OF LUTEINIZING HORMONE-BETA SUBUNIT CHLORAMPHENICOL ACETYLTRANSFERASE (LH-BETA-CAT) FUSION GENE IN RAT PITUITARY-CELLS - INDUCTION BY CYCLIC 3'-ADENOSINE MONOPHOSPHATE (CAMP) (Abstract Available)

7/6/12 (Item 10 from file: 434)
11035692 Genuine Article#: GB640 Number of References: 36 Title: THE GENE FOR THE COMMON ALPHA-SUBUNIT OF PORCINE PITUITARY %%%GLYCOPROTEIN%%% %%%HORMONE%%% (Abstract Available)

7/6/13 (Item 11 from file: 434)
10914215 Genuine Article#: FR684 Number of References: 44 Title: AMINO-TERMINAL LEUCINE-RICH REPEATS IN GONADOTROPIN RECEPTORS DETERMINE HORMONE SELECTIVITY (Abstract Available)

7/6/14 (Item 12 from file: 434)
10812386 Genuine Article#: FJ155 Number of References: 109 Title: STRUCTURE OF THE GENE ENCODING VGF, A NERVOUS SYSTEM-SPECIFIC MESSENGER-RNA THAT IS RAPIDLY AND SELECTIVELY INDUCED BY NERVE GROWTH-FACTOR IN PC12 CELLS (Abstract Available)

7/6/15 (Item 13 from file: 434)
10710886 Genuine Article#: FA907 Number of References: 52 Title: EVOLUTION OF PLACENTA-SPECIFIC GENE-EXPRESSION - COMPARISON OF THE EQUINE AND HUMAN GONADOTROPIN ALPHA-SUBUNIT GENES (Abstract Available)

7/6/16 (Item 14 from file: 434)
10613191 Genuine Article#: ET529 Number of References: 35 Title: DIFFERENT COMBINATIONS OF REGULATORY ELEMENTS MAY EXPLAIN WHY PLACENTA-SPECIFIC EXPRESSION OF THE %%%GLYCOPROTEIN%%% %%%HORMONE%%% ALPHA-SUBUNIT GENE OCCURS ONLY IN PRIMATES AND HORSES (Abstract Available)

7/6/17 (Item 15 from file: 434)
10592009 Genuine Article#: EQ593 Number of References: 56 Title: ROLE OF ERYTHROPOIETIN IN ADAPTATION TO HYPOXIA (Abstract Available)
? s hcg or fsh or lh or tsh or inhibin

22735 HCG
45501 FSH
77174 LH
37464 TSH
11209 INHIBIN
S8 155289 HCG OR FSH OR LH OR TSH OR INHIBIN
? ds

Set Items Description
S1 17 (HYBRID()PROTEIN OR CHIMERIC OR FUSION)()DIMER S2 14 RD (unique items)
S3 8820 LEUCINE()ZIPPER
S4 2225 GLYCOPROTEIN()HORMONE
S5 20 S4 AND S3
S6 17 RD (unique items)
S7 17 S6 NOT S2
S8 155289 HCG OR FSH OR LH OR TSH OR INHIBIN
? s s8 and dimerize

155289 S8
1116 DIMERIZE
S9 9 S8 AND DIMERIZE
? rd

>>>Duplicate detection is not supported for File 348.

>>>Records from unsupported files will be retained in the RD set. ...completed examining records
S10 7 RD (unique items)
? t s10/6/all

10/6/1 (Item 1 from file: 5)
13453884 BIOSIS Number: 99453884
Familial congenital hypothyroidism caused by abnormal and bioinactive %%%TSH%%% due to mutations in the beta-subunit gene
Print Number: Biological Abstracts Vol. 103 Iss. 008 Ref. 109553

10/6/2 (Item 2 from file: 5)
11215457 BIOSIS Number: 97415457
Kinetics of Fc-epsilon-RI dimer formation by specific monoclonal antibodies on mast cells
Print Number: Biological Abstracts Vol. 098 Iss. 007 Ref. 086269

10/6/3 (Item 1 from file: 348)
00446329
ORDER fax of complete patent from Dialog SourceOne. See HELP ORDER 348 MODIFIED FORMS OF REPRODUCTIVE HORMONES
MODIFIZIERTE FORMEN VON FORTPFLANZUNGSHORMONEN
FORMES MODIFIEES D'HORMONES DE REPRODUCTION
LANGUAGE (Publication,Procedural,Application): English; English; English FULLTEXT AVAILABILITY:
Available Text Language Update Word Count
CLAIMS B (English) EPAB97 1254
CLAIMS B (German) EPAB97 1187
CLAIMS B (French) EPAB97 1421
SPEC B (English) EPAB97 9420
Total word count - document A 0
Total word count - document B 13282
Total word count - documents A + B 13282

10/6/4 (Item 2 from file: 348)
00212605
ORDER fax of complete patent from Dialog SourceOne. See HELP ORDER 348 Substrate formulation in 2-amino-2-methyl-1-propanol buffer for alkaline phosphatase assays.
Substratenansatz von Mischungen in einem 2-Amino-2-methyl-1-propanil enthaltenden Puffer fur Alkalin-Phosphatase-Probe.
Formulation des substrats dans un tampon de 2-amino-2-methyle-1-propanol pour les essais d'alcaline-phosphatase.
LANGUAGE (Publication,Procedural,Application): English; English; English FULLTEXT AVAILABILITY:
Available Text Language Update Word Count
CLAIMS B (English) EPBBF1 711
CLAIMS B (German) EPBBF1 669
CLAIMS B (French) EPBBF1 761
SPEC B (English) EPBBF1 4575
Total word count - document A 0
Total word count - document B 6716
Total word count - documents A + B 6716

10/6/5 (Item 1 from file: 357)
111947 DBA Accession No.: 90-14638

Modified forms of %%%FSH%%%, %%%LH%%%, %%%HCG%%% and thyrotropin - efficiently produced and secreted in recombinant mammal cell culture; altered glycosylation and activity

10/6/6 (Item 1 from file: 434)
15617755 Genuine Article#: WU995 Number of References: 32 Title: Crystal chemistry of the copper bromide 2-aminopyrimidine system (ABSTRACT AVAILABLE)

10/6/7 (Item 2 from file: 434)
15555858 Genuine Article#: WQ020 Number of References: 73 Title: Metalloporphyrin mixed-valence pi-cation radicals: Solution stability and properties (ABSTRACT AVAILABLE)
? t s10/3,ab/3,5

>>>No matching display code(s) found in file(s): 399

10/3,AB/3 (Item 1 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS
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00446329
ORDER fax of complete patent from Dialog SourceOne. See HELP ORDER 348 MODIFIED FORMS OF REPRODUCTIVE HORMONES
MODIFIZIERTE FORMEN VON FORTPFLANZUNGSHORMONEN
FORMES MODIFIEES D'HORMONES DE REPRODUCTION
PATENT ASSIGNEE:
WASHINGTON UNIVERSITY, (645444), Campus Box 1054, One Brookings Hall, St. Louis, MO 63130, (US), (applicant designated states:
AT;BE;CH;DE;DK;ES;FR;GB;IT;LI;LU;NL;SE)
INVENTOR:
BOIME, Irving, 270 Oak Park Drive, St. Louis, MO 63141, (US) MATZUK, Martin, M., One Baylor Hospital Plaza, College of Medicine, Houston, TX 7703012, (US)
KEENE, Jeffrey, L., 8100 Leafland Court, St. Louis, MO 63123, (US) LEGAL REPRESENTATIVE:
Goldin, Douglas Michael et al (31061), J.A. KEMP & CO. 14, South Square Gray's Inn, London WC1R 5LX, (GB)
PATENT (CC, No, Kind, Date): EP 461200 A1 911218 (Basic) EP 461200 A1 921119
EP 461200 B1 970122
WO 9009800 900907
APPLICATION (CC, No, Date): EP 90905115 900220; WO 90US1037 900220 PRIORITY (CC, No, Date): US 313646 890221
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; IT; LI; LU; NL; SE INTERNATIONAL PATENT CLASS: C12P-021/00; C12P-021/02; C07K-014/59; A61K-038/24; LANGUAGE (Publication,Procedural,Application): English; English; English FULLTEXT AVAILABILITY:
Available Text Language Update Word Count
CLAIMS B (English) EPAB97 1254
CLAIMS B (German) EPAB97 1187
CLAIMS B (French) EPAB97 1421
SPEC B (English) EPAB97 9420
Total word count - document A 0
Total word count - document B 13282
Total word count - documents A + B 13282

10/3,AB/5 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs
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111947 DBA Accession No.: 90-14638 PATENT
Modified forms of %%%FSH%%%, %%%LH%%%, %%%HCG%%% and thyrotropin - efficiently produced and secreted in recombinant mammal cell culture; altered glycosylation and activity
PATENT ASSIGNEE: Washington-Univ. 1990
PATENT NUMBER: WO 9009800 PATENT DATE: 900907
WPI ACCESSION NO.: 90-290155 (9038)
PRIORITY APPLIC. NO.: US 313646 APPLIC. DATE: 890221
NATIONAL APPLIC. NO.: WO 90US1037 APPLIC. DATE: 900220
LANGUAGE: English
ABSTRACT: A modified %%%LH%%% beta subunit is claimed having enhanced activity to %%%dimerize%%% with the alpha subunit and enhanced secretion as a dimer from mammalian recombinant host cells. The subunit is a modified beta-subunit where the 7 amino acid hydrophobic sequence at positions 115-121 is deleted or replaced by a hydrophilic sequence, and at least one of Trp-8, Ile-15 and Met-42 is replaced with a hydrophilic amino acid or Thr-58 is replaced by Asn. The 115-121 sequence may be replaced by the C-terminal peptide of %%%HCG%%%. Also claimed are: (A) a DNA sequence encoding the modified %%%LH%%% beta subunit; (B) an expression system expressing the DNA and recombinant host cells containing the expression system; (C) human %%%LH%%% dimer containing the modified beta subunit; (D) an extended human %%%FSH%%% subunit in which the protein sequence of the C-terminal peptide represents positions 112-118 to 145 of %%%HCG%%% beta subunit; (E) recombinant DNA sequence, expression system and host cell; and (F) a modified human glycoprotein hormone selected from %%%FSH%%%, %%%LH%%%, %%%HCG%%% and thyrotropin in which the alpha subunit is a mutein. The modified hormones have a prolonged half-life. (65pp)
? s hormone()receptor()complex

775094 HORMONE
1146311 RECEPTOR
1230151 COMPLEX
S11 577 HORMONE()RECEPTOR()COMPLEX
? s s11 and fusion or chimeric

577 S11
270152 FUSION
38452 CHIMERIC
S12 38455 S11 AND FUSION OR CHIMERIC
? s s11 and (fusion or chimeric)

577 S11
270152 FUSION
38452 CHIMERIC
S13 19 S11 AND (FUSION OR CHIMERIC)
? r

>>>Unrecognizable Command
? rd

>>>Duplicate detection is not supported for File 348.

>>>Records from unsupported files will be retained in the RD set. ...completed examining records
S14 18 RD (unique items)
? t s14/3,ab/all

>>>No matching display code(s) found in file(s): 399

14/3,AB/1 (Item 1 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1998 BIOSIS. All rts. reserv.

11821551 BIOSIS Number: 98421551
Detailed analysis of the IL-5-IL-5R-alpha interaction: Characterization of crucial residues on the ligand and the receptor
Cornelis S; Plaetinck G; Devos R; Van Der Heyden J; Tavernier J; Sanderson C J; Guisez Y; Fiers W
Roche Res. Gent, Jozef Plateaustraat 22, 9000 Ghent, Belgium EMBO (European Molecular Biology Organization) Journal 14 (14). 1995. 3395-3402.
Full Journal Title: EMBO (European Molecular Biology Organization) Journal
ISSN: 0261-4189
Language: ENGLISH
Print Number: Biological Abstracts Vol. 100 Iss. 007 Ref. 099143 The receptor for interleukin-5 (IL-5) is composed of two different subunits. The IL-5 receptor alpha (IL-5R-alpha) is required for ligand-specific binding while association with the beta-chain results in increased binding affinity. Murine IL-5 (mIL-5) has similar activity on human and murine cells, whereas human IL-5 (hIL-5) has marginal activity on murine cells. We found that the combined substitution of K84 and N108 on hIL-5 by their respective murine counterpart yields a molecule which is as potent as mIL-5 for growth stimulation of a murine cell line. Since the unidirectional species specificity is due only to the interaction with the IL-5R-alpha subunit, we have used %%%chimeric%%% IL-5R-alpha molecules to define regions of hIL-5R-alpha involved in species-specific hIL-5 ligand binding. We found that this property is largely determined by the NH-2-terminal module of hIL-5R-alpha, and detailed analysis defined D56 and to a lesser extent E58 as important for binding. Moreover, two additional residues, D55 and Y57, were identified by alanine scanning mutagenesis within the same region. Based on the observed homology between the NH-2-terminal module and the membrane proximal (WSXWS-containing) module of hIL-5R-alpha we located this stretch of four amino acid residues (D55, D56, Y57 and E58) in the loop region that connects the C and D beta-strands on the proposed tertiary structure of the NH-2-terminal module. Finally, by comparison with residues involved in ligand binding on the elucidated structure of the growth hormone-growth %%%hormone%%% %%%receptor%%% %%%complex%%% , residue R188 on hIL-5R-alpha was identified as contributing to ligand interaction.

14/3,AB/2 (Item 1 from file: 156)
DIALOG(R)File 156:Toxline(R)
(c) format only 1998 The Dialog Corporation. All rts. reserv.
02470939 Subfile: TOXBIB-95-015035
Amino acid substitutions in the hormone-binding domain of the human androgen receptor alter the stability of the %%%hormone%%% %%%receptor%%% %%%complex%%%.
Marcelli M; Zoppi S; Wilson CM; Griffin JE; McPhaul MJ
Department of Internal Medicine, University of Texas Southwestern Medical Center at Dallas 75235-8857.
Source: J Clin Invest; VOL 94, ISS 4, 1994, P1642-50 ISSN: 0021-9738 Coden: HS7
Language: ENGLISH
Document Type: JOURNAL ARTICLE
We have investigated the basis of androgen resistance in seven unrelated individuals with complete testicular feminization or Reifenstein syndrome caused by single amino acid substitutions in the hormone-binding domain of the androgen receptor. Monolayer-binding assays of cultured genital skin fibroblasts demonstrated absent ligand binding, qualitative abnormalities of androgen binding, or a decreased amount of qualitatively normal receptor. The consequences of these mutations were examined by introducing the mutations by site-directed mutagenesis into the androgen receptor cDNA sequence and expressing the mutant cDNAs in mammalian cells. The effects of the amino acid substitutions on the binding of different androgens and on the capacity of the ligand-bound receptors to activate a reporter gene were investigated. Substantial differences were found in the responses of the mutant androgen receptors to incubation with testosterone, 5 alpha-dihydrotestosterone, and mibolerone. In several instances, increased doses of hormone or increased frequency of hormone addition to the incubation medium resulted in normal or near normal activation of a reporter gene by cells expressing the mutant androgen receptors. These studies suggest that the stability of the %%%hormone%%% %%%receptor%%% %%%complex%%% is a major determinant of receptor function in vivo.

14/3,AB/3 (Item 2 from file: 156)
DIALOG(R)File 156:Toxline(R)
(c) format only 1998 The Dialog Corporation. All rts. reserv.
01961006 Subfile: TOXBIB-94-158900
Identification of charged residues in an N-terminal portion of the hormone-binding domain of the human estrogen receptor important in transcriptional activity of the receptor.
Pakdel F; Reese JC; Katzenellenbogen BS
Department of Physiology and Biophysics, University of Illinois, Urbana 61801.
Source: Mol Endocrinol; VOL 7, ISS 11, 1993, P1408-17 ISSN: 0888-8809 Coden: NGZ
Language: ENGLISH
Document Type: JOURNAL ARTICLE
We have shown that charged amino acids near C530 of the human estrogen receptor (ER) are involved in receptor discrimination between estrogen and antiestrogen. We now examine the role of charged residues, adjacent to the three other cysteines (381, 417, and 447) in the hormone-binding domain of the human ER, in the hormone-binding, DNA-binding, and transcription activation abilities of the receptor. Mutation of the one charged amino acid nearest to C381 gave a mutant receptor (E380Q) requiring two to three times less estradiol (E2) than wild type (WT) ER to achieve maximal activity and having activity in the absence of added estrogen that was 6-fold higher than that of WT receptor. The enhanced ability of this mutant to bind to estrogen response element DNA in the absence and presence of estrogen may, at least in part, explain its elevated, seemingly constitutive trans-activation activity and its increased sensitivity to estrogen. While more sensitive to E2, this E380Q mutant was less sensitive than WT ER to antiestrogen for suppression of transcriptional activity. Mutation of all three charged residues nearest to C381 (the triple mutant D374N, E380Q, and E385Q) resulted in a greatly reduced potency of the receptor in trans-activation with no change in estrogen-binding affinity. When K449 (near C447), highly conserved among steroid receptors, was mutated to Q, 400-fold more E2 was required for maximal reporter gene trans-activation due to an unstable, temperature-sensitive %%%hormone%%%- %%%receptor%%% %%%complex%%%. In contrast, the mutant K416Q (near C417) was unaltered in E2-binding or receptor transcriptional activity. These studies reveal a region in the N-terminal portion of the hormone-binding domain (ca. amino acids

374-385) where alterations in charged residues result in either increases or decreases in receptor transcriptional activity with no change in receptor affinity for hormone. Our findings suggest that this region may be important in DNA binding and protein-protein interactions that modulate transcriptional activity of the ER. In addition, the region near C447, which is well conserved among steroid receptors, appears to be important in maintaining the receptor in a conformation that is stable at physiological (37 C) temperatures. To our knowledge, this is the first report of an ER (E380Q) with a sensitivity to E2 for trans-activation greater than that of WT receptor and having high trans-activation activity in the absence of added hormone.

14/3,AB/4 (Item 1 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS
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00871466
ORDER fax of complete patent from Dialog SourceOne. See HELP ORDER 348 Estrogen receptor
Ostrogen-Rezeptor
Recepteur d'oestrogene
PATENT ASSIGNEE:
Akzo Nobel N.V., (200754), Velperweg 76, 6824 BM Arnhem, (NL), (applicant designated states:

AT;BE;CH;DE;DK;ES;FI;FR;GB;GR;IE;IT;LI;LU;MC;NL;PT;SE) INVENTOR:
Mosselman, Sietse, De Edelenburg 34, 5346 VM OSS, (NL)
Dijkema, Rein, Pensionarisstraat 6, 5345 ML Oss, (NL)
LEGAL REPRESENTATIVE:
Ogilvie-Emanuelson, Claudia Maria et al (80441), Patent Department Pharma N.V. Organon P.O. Box 20, 5340 BH Oss, (NL)
PATENT (CC, No, Kind, Date): EP 798378 A2 971001
(Basic) EP 798378 A3 971229
APPLICATION (CC, No, Date): EP 97200903 970325;
PRIORITY (CC, No, Date): EP 96203284 961122; EP 96200820 960326 DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
INTERNATIONAL PATENT CLASS: C12N-015/12; C12N-015/62; C12N-015/85; C07K-014/72; C12N-001/21; C12N-005/16; C12Q-001/00; C12Q-001/68;
ABSTRACT EP 798378 A2
The present invention relates to isolated DNA encoding novel estrogen receptors, the proteins encoded by said DNA, %%%chimeric%%% receptors comprising parts of said novel receptors and uses thereof. ABSTRACT WORD COUNT: 29

LANGUAGE (Publication,Procedural,Application): English; English; English FULLTEXT AVAILABILITY:
Available Text Language Update Word Count
CLAIMS A (English) 9709W4 548
SPEC A (English) 9709W4 7171
Total word count - document A 7719
Total word count - document B 0
Total word count - documents A + B 7719

14/3,AB/5 (Item 2 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS
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00809770
ORDER fax of complete patent from Dialog SourceOne. See HELP ORDER 348 Expression vectors that produce steroid receptors, steroid receptor chimera, screening assays for steroid receptors and clinical assays using synthesized recept
Expressionsvektoren die Steroidrezeptoren produzieren, Steroidrezeptoren-Ch imaren, Screeningtests fur Steroidrezeptoren und Verwendung der so hergestellten Reze
Vecteurs d'expression pour la production de recepteurs steroides, chimeres de ces recepteurs, tests de depistage pour ces recepteurs et tests cliniques utilisan
PATENT ASSIGNEE:
BAYLOR COLLEGE OF MEDICINE, (401891), One Baylor Plaza, Houston, TX 77030 , (US), (applicant designated states:
AT;BE;CH;DE;DK;ES;FR;GB;IT;LI;NL;SE)
INVENTOR:
McDonnell, Donald, P., 1246 Manchester Circle, Missouri City, Texas 77459 , (US)
O'Malley, Bert W., 629 Ramblewood, Houston, Texas 77079, (US) Coneely, Orla M., 7350 Kirby Drive 17, Houston, Texas 77030, (US) LEGAL REPRESENTATIVE:
Wise, Stephen James et al (46011), c/o RAWORTH, MOSS & COOK 36 Sydenham Road, Croydon, Surrey CR0 2EF, (GB)
PATENT (CC, No, Kind, Date): EP 752477 A2 970108
(Basic) EP 752477 A3 970514
APPLICATION (CC, No, Date): EP 96110474 910115;
PRIORITY (CC, No, Date): US 464837 900116; US 639506 910109 DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; IT; LI; NL; SE INTERNATIONAL PATENT CLASS: C12Q-001/68;

ABSTRACT EP 752477 A2
The present invention relates to a method for making an expression vector which produces a biological active receptor. The method includes synthesizing a linker having the carboxyl six amino acids of ubiquitin and an internal restriction site and cloning the synthesized linker to form a plasmid. The plasmid is then digested with a restriction endonuclease which is compatible with the internal restriction site in the synthesized linker. After the digestion of the plasmid a cDNA coding for the receptor is inserted into the compatible restriction site and the plasmid is then used to transform yeast. In the procedure, the yeast that is usually used is from the strains of Saccharomyce and Aspergillus. In addition, numerous vectors which express the human vitamin D receptor, human androgen receptor, human progesterone receptor, thyroid receptor, retinoic acid receptor, chicken progesterone receptor, chicken vitamin D receptor, rat vitamin D receptor and COUP protein are described. A further aspect of the invention is the reporter vector which includes the proximal promoter element of the yeast iso-l-cytochrome C and a structural gene selected from E. coli either the o-Galactosidase gene or the Galactokinase gene. The reporter vector is used to detect for agonist and antagonists for the steroid hormone receptor. A further element of the invention is a chimera made up of the DNA binding domain from one receptor and the hormone binding domain from another receptor. The chimera is used in an assay to identify the function of the unknown receptor component. Additional aspects are clinical and laboratory assays for biological compounds using the receptors synthesized from the expression vectors and using receptor vectors.
ABSTRACT WORD COUNT: 269

LANGUAGE (Publication,Procedural,Application): English; English; English FULLTEXT AVAILABILITY:
Available Text Language Update Word Count
CLAIMS A (English) EPAB97 1033
SPEC A (English) EPAB97 8829

Total word count - document A 9862
Total word count - document B 0
Total word count - documents A + B 9862

14/3,AB/6 (Item 3 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS
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00785892
ORDER fax of complete patent from Dialog SourceOne. See HELP ORDER 348 Hormone receptor compositions and methods
Hormon-Rezeptorverbindungen und Methoden
Compositions receptrices d'hormones et procedes
PATENT ASSIGNEE:
THE SALK INSTITUTE FOR BIOLOGICAL STUDIES, (273851), 10010 North Torrey Pines Road, La Jolla California 92037, (US), (applicant designated states: AT;BE;CH;DE;FR;GB;IT;LI;LU;NL;SE)
INVENTOR:
Evans, Ronald M., 3702 Clark Street, San Diego, Cifornia 92100, (US) Weinberger, Gary A., 12620 Dalewood Drive, Silver Spring, Maryland 20906, (US)
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Arriza, Jeffrey Louis, 331 Redwood, Carlsbad, California 92008, (US) Thompson, Catherine Caroline, 3903 Miramar Street, LaJolla, California 92037, (US)
Ong, Estelita Sebastian, 6307 Hannon Court, San Diego, California 92117, (US)
LEGAL REPRESENTATIVE:
Kolb, Helga, Dr. Dipl.-Chem. et al (49372), Hoffmann, Eitle & Partner, Patent-und Rechtsanwalte, Arabellastrasse 4, 81925 Munchen, (DE) PATENT (CC, No, Kind, Date): EP 733705 A1 960925 (Basic) APPLICATION (CC, No, Date): EP 95120305 871023;
PRIORITY (CC, No, Date): US 922585 861024; US 108471 871020 DESIGNATED STATES: AT; BE; CH; DE; FR; GB; IT; LI; LU; NL; SE INTERNATIONAL PATENT CLASS: C12N-015/12; C07K-014/72; C12N-015/70; C12N-001/21; C12N-005/10; C12Q-001/68;

ABSTRACT EP 733705 A1
Substantially pure DNA and plasmids containing the DNA which is comprised of sequences which encode proteins having hormone-binding and/or transcription-activating characteristics of a thyroid hormone. The invention further provides receptor proteins and modified functional forms for producing desired proteins in genetically engineered cells. One method involves inducing transcription of a gene whose transcription is activated by hormones complexed with receptors; the second is a method for engineering a cell and increasing and controlling production of a protein encoded by a gene whose transcription is activated by hormones complexed with receptor proteins.
ABSTRACT WORD COUNT: 109

LANGUAGE (Publication,Procedural,Application): English; English; English FULLTEXT AVAILABILITY:
Available Text Language Update Word Count
CLAIMS A (English) EPAB96 828
SPEC A (English) EPAB96 42784
Total word count - document A 43612
Total word count - document B 0
Total word count - documents A + B 43612

14/3,AB/7 (Item 4 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS
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00632922
ORDER fax of complete patent from Dialog SourceOne. See HELP ORDER 348 Glycoprotein hormone receptor molecules.
Glykoprotein-Hormonrezeptor-Molekule.
Molecules receptrices d'hormone de glycoproteine.
PATENT ASSIGNEE:
GENENTECH, INC., (210480), 460 Point San Bruno Boulevard, South San Francisco California 94080, (US), (applicant designated states: AT;BE;CH;DE;DK;ES;FR;GB;IT;LI;LU;NL;SE)
INVENTOR:
Nikolics, Karoly, 209 Club Drive, San Carlos, California 94070, (US) Mcfarland, Keith C., 1905 Berryman Street, Berkeley, California 94709, (US)
Segaloff, Deborah L., 28 Hunters Court, Iowa City Iowa 52240, (US) Seeburg, Peter H., 5, Erzackerweg, D-6900 Heidelberg, (DE) LEGAL REPRESENTATIVE:
Armitage, Ian Michael et al (27761), MEWBURN ELLIS York House 23 Kingsway , London WC2B 6HP, (GB)
PATENT (CC, No, Kind, Date): EP 614975 A1 940914 (Basic) APPLICATION (CC, No, Date): EP 94104166 900504;
PRIORITY (CC, No, Date): US 347683 890505
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; IT; LI; LU; NL; SE INTERNATIONAL PATENT CLASS: C12N-015/12; C12N-001/21; C12N-005/10; C07K-013/00;

ABSTRACT EP 614975 A1
The invention relates to the purification, and cloning of receptors for the luteinizing hormone, choriogonadotropin, follicle stimulating hormone, and thyroid stimulating hormone. The invention additionally concerns the uses for such molecules in the diagnosis and therapy of human conditions.
ABSTRACT WORD COUNT: 41

LANGUAGE (Publication,Procedural,Application): English; English; English FULLTEXT AVAILABILITY:
Available Text Language Update Word Count
CLAIMS A (English) EPABF2 407
SPEC A (English) EPABF2 25992
Total word count - document A 26399
Total word count - document B 0
Total word count - documents A + B 26399

14/3,AB/8 (Item 5 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS
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00479675
ORDER fax of complete patent from Dialog SourceOne. See HELP ORDER 348 Expression vectors that produce steroid receptors, steroid receptor chimera, screening assays for steroid receptors and clinical assays using synthesized recept
Expressionsvektoren die Steroidrezeptoren produzieren, Steroidrezeptoren-Ch imaren, Screeningtests fur Steroidrezeptoren und Verwendung der so hergestellten Reze
Vecteurs d'expression pour la production de recepteurs steroides, chimeres de ces recepteurs, tests de depistage pour ces recepteurs et tests cliniques utilisan
PATENT ASSIGNEE:
BAYLOR COLLEGE OF MEDICINE, (401891), One Baylor Plaza, Houston, TX 77030 , (US), (applicant designated

states:
AT;BE;CH;DE;DK;ES;FR;GB;IT;LI;NL;SE)
INVENTOR:
McDonnell, Donald P., 1246 Manchester Circle, Missouri City, Texas 77459, (US)
O'Malley, Bert W., 629 Ramblewood, Houston, Texas 77079, (US) Conneely, Orla M., 7350 Kirby Drive 17, Houston, Texas 77030, (US) LEGAL REPRESENTATIVE:
Adams, William Gordon et al (27554), RAWORTH, MOSS & COOK 36 Sydenham Road, Croydon Surrey CR0 2EF, (GB)
PATENT (CC, No, Kind, Date): EP 441483 A2 910814
(Basic) EP 441483 A3 921119
APPLICATION (CC, No, Date): EP 91300287 910115;
PRIORITY (CC, No, Date): US 464837 900116; US 639506 910109 DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; IT; LI; NL; SE INTERNATIONAL PATENT CLASS: C12N-015/12; C12N-015/81; C12N-001/19; G01N-033/58; G01N-033/68; C12Q-001/68; C12Q-001/34; C12Q-001/48;
ABSTRACT EP 441483 A2

The present invention relates to a method for making an expression vector which produces a biological active receptor. The method includes synthesizing a linker having the carboxyl six amino acids of ubiquitin and an internal restriction site and cloning the synthesized linker to form a plasmid. The plasmid is then digested with a restriction endonuclease which is compatible with the internal restriction site in the synthesized linker. After the digestion of the plasmid a cDNA coding for the receptor is inserted into the compatible restriction site and the plasmid is then used to transform yeast. In the procedure, the yeast that is usually used is from the strains of Saccharomyce and Aspergillus. In addition, numerous vectors which express the human vitamin D receptor, human androgen receptor, human progesterone receptor, thyroid receptor, retinoic acid receptor, chicken progesterone receptor, chicken vitamin D receptor, rat vitamin D receptor and COUP protein are described. A further aspect of the invention is the reporter vector which includes the proximal promoter element of the yeast iso-I-cytochrome C and a structural gene selected from E. coli either the o-Galactosidase gene or the Galactokinase gene. The reporter vector is used to detect for agonist and antagonists for the steroid hormone receptor. A further element of the invention is a chimera made up of the DNA binding domain from one receptor and the hormone binding domain from another receptor. The chimera is used in an assay to identify the function of the unknown receptor component. Additional aspects are clinical and laboratory assays for biological compounds using the receptors synthesized from the expression vectors and using receptor vectors. (see image in original document)
ABSTRACT WORD COUNT: 275

LANGUAGE (Publication,Procedural,Application): English; English; English FULLTEXT AVAILABILITY:
Available Text Language Update Word Count
CLAIMS A (English) EPABF1 1436
SPEC A (English) EPABF1 8918
Total word count - document A 10354
Total word count - document B 0
Total word count - documents A + B 10354

14/3,AB/9 (Item 6 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS
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00450316
ORDER fax of complete patent from Dialog SourceOne. See HELP ORDER 348 GAMMA RETINOIC ACID RECEPTOR
GAMMA-RETINOINSAURE-REZEPTOR
RECEPTEUR D'ACIDE GAMMA RETINOIQUE
PATENT ASSIGNEE:
THE SALK INSTITUTE FOR BIOLOGICAL STUDIES, (273851), 10010 North Torrey Pines Road, La Jolla California 92037, (US), (applicant designated states: AT;BE;CH;DE;ES;FR;GB;IT;LI;LU;NL;SE)
Sloan-Kettering Institute For Cancer Research, (239590), 1275 York Avenue , New York, New York 10021, (US), (applicant designated states: AT;BE;CH;DE;ES;FR;GB;IT;LI;LU;NL;SE)
TAKAKU, Fumimaro, (1467990), 1-43, Asahigaoka, Nerima-ku, Tokyo, (JP), (applicant designated states: AT;BE;CH;DE;ES;FR;GB;IT;LI;LU;NL;SE) IMAWARI, Michio, (1468000), 30-8-207, Motoyoyogi-cho, Shibuya-ku, Tokyo, (JP), (applicant designated states: AT;BE;CH;DE;ES;FR;GB;IT;LI;LU;NL;SE)
ISHIKAWA, Takashi, (1468020), 8 Locksley, No. 6K, San Francisco, CA 94122 , (US), (applicant designated states: AT;BE;CH;DE;ES;FR;GB;IT;LI;LU;NL;SE)
INVENTOR:
TAKAKU, Fumimaro, 1-43, Asahigaoka Nerima-ku, Tokyo, (JP) IMAWARI, Michio, 30-8-207, Motoyoyogi-cho, Shibuya-ku, Tokyo, (JP) ISHIKAWA, Takashi, 8 Locksley, no. 6K, San Francisco, CA 94122, (US) EVANS, Ronald Mark, 8615 La Jolla Scenic Drive, La Jolla, CA 92037, (US) UMESONO, Kazuhiko, 7451 East Herschel Avenue, La Jolla, CA 92037, (US) LEGAL REPRESENTATIVE:
Kolb, Helga, Dr. Dipl.-Chem. et al (49371), Hoffmann, Eitle & Partner, Patentanwalte, Postfach 81 04 20, 81904 Munchen, (DE)
PATENT (CC, No, Kind, Date): EP 479916 A1 920415
(Basic) EP 479916 A1 921007
EP 479916 B1 961120
WO 9015815 901227
APPLICATION (CC, No, Date): EP 90911356 900622; WO 90US3564 900622 PRIORITY (CC, No, Date): US 370407 890622
DESIGNATED STATES: AT; BE; CH; DE; ES; FR; GB; IT; LI; LU; NL; SE INTERNATIONAL PATENT CLASS: C07K-014/705;
LANGUAGE (Publication,Procedural,Application): English; English; English FULLTEXT AVAILABILITY:
Available Text Language Update Word Count
CLAIMS B (English) EPAB96 624
CLAIMS B (German) EPAB96 499
CLAIMS B (French) EPAB96 718
SPEC B (English) EPAB96 3778
Total word count - document A 0
Total word count - document B 5619
Total word count - documents A + B 5619

14/3,AB/10 (Item 7 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS
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00448489
ORDER fax of complete patent from Dialog SourceOne. See HELP ORDER 348 GLYCOPROTEIN HORMONE RECEPTOR MOLECULES.
GLYKOPROTEIN-HORMONREZEPTOR-MOLEKULE.
MOLECULES RECEPTRICES D'HORMONE DE GLYCOPROTEINE.
PATENT ASSIGNEE:
GENENTECH, INC., (210480), 460 Point San Bruno Boulevard, South San Francisco California 94080, (US), (applicant designated states: AT;BE;CH;DE;DK;ES;FR;GB;IT;LI;LU;NL;SE)
INVENTOR:

NIKOLICS, Karoly, 209 Club Drive, San Carlos, CA 94070, (US) MCFARLAND, Keith, C., 1905 Berryman Street, Berkeley, CA 94709, (US) SEGALOFF, Deborah, L., 661 Tilden Avenue, Teaneck, NJ 07666, (US) SEEBURG, Peter, H., 5, Erzackerweg, D-6900 Heidelberg, (DE) LEGAL REPRESENTATIVE:
Armitage, Ian Michael et al (27762), MEWBURN ELLIS York House 23 Kingsway , London WC2B 6HP, (GB)
PATENT (CC, No, Kind, Date): EP 471030 A1 920219 (Basic) EP 471030 B1 941214
WO 9013643 901115
APPLICATION (CC, No, Date): EP 90908349 900504; WO 90US2488 900504 PRIORITY (CC, No, Date): US 347683 890505
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; IT; LI; LU; NL; SE INTERNATIONAL PATENT CLASS: A61K-037/02;
LANGUAGE (Publication,Procedural,Application): English; English; English FULLTEXT AVAILABILITY:
Available Text Language Update Word Count
CLAIMS B (English) EPBBF1 487
CLAIMS B (German) EPBBF1 390
CLAIMS B (French) EPBBF1 587
SPEC B (English) EPBBF1 23108
Total word count - document A 0
Total word count - document B 24572
Total word count - documents A + B 24572

14/3,AB/11 (Item 8 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS
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00323537
ORDER fax of complete patent from Dialog SourceOne. See HELP ORDER 348 Retinoic acid receptor and derivatives thereof, DNA encoding either substance and use of the proteins and of the DNA
Retinoesaurerezeptor und Derivate davon, beide Substanzen codierende DNS und die Verwendung der Proteine und der DNS
Recepteur de l'acide retinoique et ses derivees, DNA codant pour ces deux substances et l'usage des proteines et des DNA
PATENT ASSIGNEE:
INSTITUT PASTEUR, (250791), 28, rue du Docteur Roux, F-75715 Paris Cedex 15, (FR), (applicant designated states: AT;BE;CH;DE;ES;FR;GB;GR;IT;LI;LU;NL;SE)
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Dejean, Anne, 6 rue Nansouty, F-75014 Paris, (FR)
Blaudin de The, Hugues, 28 rue Rambuteau, F-75003 Paris, (FR) Marchio, Agnes, 121 rue de Montreuil, F-75011 Paris, (FR) LEGAL REPRESENTATIVE:
Gutmann, Ernest et al (15992), Ernest Gutmann - Yves Plasseraud S.A. 3, rue Chauveau-Lagarde, 75008 Paris, (FR)
PATENT (CC, No, Kind, Date): EP 321362 A1 890621 (Basic) EP 321362 B1 960925
APPLICATION (CC, No, Date): EP 88403229 881216; PRIORITY (CC, No, Date): US 133687 871216; US 134130 871217; US 209009 880620; US 278136 881130
DESIGNATED STATES: AT; BE; CH; DE; ES; FR; GB; GR; IT; LI; LU; NL; SE INTERNATIONAL PATENT CLASS: C12N-015/12; C12P-021/02; C12Q-001/68; C07K-014/00;

ABSTRACT EP 321362 A1
A previously isolated hepatitis B virus (HBV) integration in a 147 bp cellular DNA fragment linked to hepatocellular carcinoma (HCC) was used as a probe to clone the corresponding complementary DNA from a human liver cDNA library. Nucleotide sequence analysis revealed that the overall structure of the cellular gene, which has been named hap, is similar to that of the DNA-binding hormone receptors. Six out of seven hepatoma and hepatoma-derived cell-lines express a 2.5 kb hap mRNA species which is undetectable in normal adult and fetal livers, but present in all non-hepatic tissues analyzed. Low stringency hybridization experiments revealed the existence of hap related genes in the human genome. The cloned DNA sequence is useful in the preparation of pure hap protein and as a probe in the detection and isolation of complementary DNA and RNA sequences. The hap protein is a retinoic acid (RA) receptor identified as RAR-b.
ABSTRACT WORD COUNT: 153

LANGUAGE (Publication,Procedural,Application): English; English; English FULLTEXT AVAILABILITY:
Available Text Language Update Word Count
CLAIMS A (English) EPABF1 685
CLAIMS B (English) EPAB96 823
CLAIMS B (German) EPAB96 759
CLAIMS B (French) EPAB96 914
SPEC A (English) EPABF1 13581
SPEC B (English) EPAB96 13659
Total word count - document A 14268
Total word count - document B 16155
Total word count - documents A + B 30423

14/3,AB/12 (Item 9 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS
(c) 1998 EUROPEAN PATENT OFFICE. All rts. reserv.

00319376
ORDER fax of complete patent from Dialog SourceOne. See HELP ORDER 348 Retinoic acid receptor composition and method for identifying ligands.
Retinoesaure-Rezeptor-Komposition und Verfahren zur Ligand-Identifizierung. Composition de recepteur de l'acide retinoique et procede d'identification de ligands.
PATENT ASSIGNEE:
THE SALK INSTITUTE FOR BIOLOGICAL STUDIES, (273851), 10010 North Torrey Pines Road, La Jolla California 92037, (US), (applicant designated states: AT;BE;CH;DE;ES;FR;GB;GR;IT;LI;LU;NL;SE)
INVENTOR:
Evans, Ronald Mark,, 8615 La Jolla Scenic Drive North,, La Jolla, CA 92037, (US)
Giguere, Vincent,, 1320 Islington Avenue, Apt. 606,, Etobicoke, Ontario M9A 5C6, (CA)
Ong, Estelita Sebastian,, 6307 Hannon Court, San Diego, CA 92117, (US) Segui, Prudimar Serrano, 22574 Windcrest Lane, San Diego, CA 92128, (US) Umesono, Kazuhiko,, 4178 Decoro Street, No. 60, San Diego, CA 92122, (US)
Thompson, Catherine Caroline, 1325 West 42nd Street, Baltimore, Maryland 21211, (US)
LEGAL REPRESENTATIVE:
Kolb, Helga, Dr. Dipl.-Chem. et al (49371), Hoffmann, Eitle & Partner, Patentanwalte, Postfach 81 04 20, D-81904 Munchen, (DE) PATENT (CC, No, Kind, Date): EP 325849 A2 890802 (Basic) EP 325849 A3 911016
EP 325849 B1 950705
APPLICATION (CC, No, Date): EP 88311477 881202; PRIORITY (CC, No, Date): US 128331 871202; US 276536 881130 DESIGNATED STATES: AT; BE; CH; DE; ES; FR; GB; GR; IT; LI; LU; NL; SE INTERNATIONAL PATENT CLASS: C12N-015/12; C12P-021/02; C12N-015/62;

C12N-005/10; C12Q-001/68;

ABSTRACT EP 325849 A2

A novel retinoic acid receptor is disclosed. The novel receptor is encoded for by cDNA carried on plasmid phRAR1, which has been deposited with the American Type Culture Collection for patent purposes. %%%Chimeric%%% receptor proteins are also disclosed. The chimera are constructed by exchanging functional domains between the glucocorticoid, the mineralocorticoid, the estrogen-related, the thyroid and the retinoic acid receptors. In addition, a novel method for identifying functional ligands for receptor proteins is disclosed. The method, which takes advantage of the modular structure of the hormone receptors and the idea that the functional domains may be interchangeable, replaces the DNA-binding domain of a putative novel receptor with the DNA-binding domain of a known receptor such as the glucocorticoid receptor. The resulting %%%chimeric%%% construction, when expressed in cells, produces a hybrid receptor whose activation of a ligand-(e.g., glucocorticoid) inducible promoter is dependent on the presence of the new ligand. The novel method is illustrated in part by showing that the ligand for the new receptor protein is the retinoid, retinoic acid.

ABSTRACT WORD COUNT: 174

LANGUAGE (Publication,Procedural,Application): English; English; English FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	EPABF1	1278
CLAIMS B	(English)	EPAB95	2782
CLAIMS B	(German)	EPAB95	2645
CLAIMS B	(French)	EPAB95	3435
SPEC A	(English)	EPABF1	12129
SPEC B	(English)	EPAB95	12247

Total word count - document A 13408
Total word count - document B 21109
Total word count - documents A + B 34517

14/3,AB/13 (Item 10 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS
(c) 1998 EUROPEAN PATENT OFFICE. All rts. reserv.

00221880
ORDER fax of complete patent from Dialog SourceOne. See HELP ORDER 348 %%%Chimeric%%% plasmid vector.
Chimarer Plasmidvektor.
Vecteur chimerique de plasmide.
PATENT ASSIGNEE:
KABUSHIKI KAISHA YAKULT HONSHA, (316160), 1-19, Higashishinbashi 1-chome, Minato-ku Tokyo 105, (JP), (applicant designated states: AT;BE;CH;DE;FR;GB;IT;LI;LU;NL;SE)
INVENTOR:
Shirasawa, Yukio, 201, 2-1-7, Ojima Chofu, Tokyo, (JP)
Tsuchida, Nobuo, 2-29-47, Kashiwa-cho Shiki, Saitama, (JP)
LEGAL REPRESENTATIVE:
Brewer, Leonard Stuart et al (42871), SANDERSON & CO. European Patent Attorneys 34, East Stockwell Street, Colchester Essex CO1 1ST, (GB) PATENT (CC, No, Kind, Date): EP 219214 A1 870422 (Basic) EP 219214 B1 920408
APPLICATION (CC, No, Date): EP 86306714 860829;
PRIORITY (CC, No, Date): JP 85191427 850830
DESIGNATED STATES: AT; BE; CH; DE; FR; GB; IT; LI; LU; NL; SE INTERNATIONAL PATENT CLASS: C12N-015/85;

ABSTRACT EP 219214 A1

%%%Chimeric%%% plasmid vector.

A %%%chimeric%%% plasmid vector comprising first to fifth DNA fragments, wherein the first DNA fragment has a first LTR region derived from an MMTV and a 5(min)-splicing site located downstream of the first LTR region and the second DNA fragment has a 3(min)-splicing site derived from plasmid pCVSVE and located immediately downstream of the first DNA fragment, which second DNA fragment is followed by a polylinker derived from plasmid pi-AN7. The first LTR region of the first DNA fragment comprises a hormone dependent region (or a %%%hormone%%% %%%receptor%%% %%%complex%%% binding region) and an MMTV promotor region located downstream of the hormone dependent region, The third DNA fragment has a second LTR region derived from an MMN and having an transcription termination site, while the fourth DNA fragment comprises an SV40 promotor region derived from plasmid pSV2gpt and an Eco-gpt gene region derived from the plasmid pSV2gpt and operable as a gene marker. The first and fourth DNA fragments are linked together through the fifth DNA fragment which comprises an ampicillin resistance gene region derived from plasmid pBR332 and a replication origin derived from the plasmid pBR332.

ABSTRACT WORD COUNT: 191

LANGUAGE (Publication,Procedural,Application): English; English; English FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS B	(English)	EPBBF1	467
CLAIMS B	(German)	EPBBF1	449
CLAIMS B	(French)	EPBBF1	514
SPEC B	(English)	EPBBF1	5807

Total word count - document A 0
Total word count - document B 7237
Total word count - documents A + B 7237

14/3,AB/14 (Item 1 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
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14023503 Genuine Article#: RK331 Number of References: 49 Title: CRYSTAL-STRUCTURE OF A COMPLEX BETWEEN INTERFERON-GAMMA AND ITS SOLUBLE HIGH-AFFINITY RECEPTOR
Author(s): WALTER MR; WINDSOR W; NAGABHUSHAN TL; LUNDELL DJ; LUNN CA; ZAUODNY PJ; NARULA SK
Corporate Source: UNIV ALABAMA,DEPT PHARMACOL/BIRMINGHAM//AL/35294; UNIV ALABAMA,CTR MACROMOLEC CRYSTALLOG/BIRMINGHAM//AL/35294; SCHERING PLOUGH CORP,RES INST/KENILWORTH//NJ/07033
Journal: NATURE, 1995, V376, N6537 (JUL 20), P230-235
ISSN: 0028-0836
Language: ENGLISH Document Type: ARTICLE
Abstract: The crystal structure of interferon-gamma bound to the extracellular fragment of its high-affinity cell-surface receptor reveals the first view of a class-2 cytokine receptor-ligand complex. In the complex, one interferon-gamma homodimer binds two receptor molecules. Unlike the class-1 growth %%%hormone%%% %%%receptor%%% %%%complex%%%, the two interferon-gamma receptors do not interact with one another and are separated by 27 Angstrom. Upon receptor binding, the flexible As loop of interferon-gamma undergoes a conformational change that includes the formation of a 3(10) helix.

14/3,AB/15 (Item 2 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
(c) 1998 Inst for Sci Info. All rts. reserv.

14000492 Genuine Article#: RG360 Number of References: 6 Title: STRUCTURAL AND FUNCTIONAL EPITOPES IN THE GROWTH-%%%HORMONE%%% %%%RECEPTOR%%% %%%COMPLEX%%%
Author(s): WELLS JA
Corporate Source: GENENTECH INC,460 SAN BRUNO BLVD/S SAN FRANCISCO//CA/94080
Journal: BIO-TECHNOLOGY, 1995, V13, N7 (JUL), P647-651
ISSN: 0733-222X
Language: ENGLISH Document Type: ARTICLE

14/3,AB/16 (Item 3 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
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13967661 Genuine Article#: RD907 Number of References: 12 Title: STRUCTURE OF THE GROWTH %%%HORMONE%%%-%%%RECEPTOR%%% %%%COMPLEX%%% AND MECHANISM OF RECEPTOR SIGNALING
Author(s): KOSSIAKOFF AA
Corporate Source: GENENTECH INC,DEPT PROT ENGN,460 POINT SAN BRUNO BLVD/S SAN FRANCISCO//CA/94080
Journal: JOURNAL OF NUCLEAR MEDICINE, 1995, V36, N6 (JUN), PS14-S16 ISSN: 0161-5505
Language: ENGLISH Document Type: ARTICLE
Abstract: The structure of the growth %%%hormone%%%-%%%receptor%%% %%%complex%%% discussed here is the first such system to be studied at the level of atomic detail and provides unique information that elucidates the mechanism of signal transduction of an important receptor family. The growth hormone receptor is a single-pass receptor, with an extracellular protein domain, a transmembrane domain and an intracellular protein domain. Structural data, obtained by crystallography, indicate that there are actually two growth hormone receptors that encapsulate the bound hormone. Although the topology of the hormone is asymmetric, the receptors can use their same sequence of residues to bind to different structural motifs by changing conformation. This mechanism of aggregation controls signal transduction. It may be possible to use this information in the design of radiolabeled ligands for molecular nuclear medicine studies involving the concentration or occupancy of growth receptors.

14/3,AB/17 (Item 4 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
(c) 1998 Inst for Sci Info. All rts. reserv.

13683472 Genuine Article#: QH590 Number of References: 32 Title: STOICHIOMETRY OF THE ATRIAL NATRIURETIC FACTOR-R1 RECEPTOR COMPLEX IN THE BOVINE ZONA GLOMERULOSA
Author(s): RONDEAU JJ; MCNICOLL N; GAGNON J; BOUCHARD N; ONG H; DELEAN A Corporate Source: UNIV MONTREAL,DEPT PHARMACOL/MONTREAL/PQ H3C 3J7/CANADA/; UNIV MONTREAL,DEPT PHARMACOL/MONTREAL/PQ H3C 3J7/CANADA/; UNIV MONTREAL,FAC PHARM/MONTREAL/PQ H3C 3J7/CANADA/; CEA/GRENOBLE//FRANCE/; CNRS,URA 1333/GRENOBLE//FRANCE/
Journal: BIOCHEMISTRY, 1995, V34, N7 (FEB 21), P2130-2136
ISSN: 0006-2960
Language: ENGLISH Document Type: ARTICLE
Abstract: The atrial natriuretic R1 receptor is a membrane protein that is present as an apparently preassociated noncovalent oligomer in the absence of ligand as suggested by steric exclusion studies and cross-linking experiments in physiological and recombinant receptor expression systems. The association state of this receptor oligomer was studied in the presence of amiloride and ATP, two known modulators of the R1 receptor functions with both the intact receptor and a cytoplasmic domain-deleted form obtained by limited proteolysis with trypsin, It was shown by steric exclusion on Superose 6 column that amiloride increased the affinity of ANF for the native and truncated receptor, in contrast with ATP, whose destabilizing effect on ANF binding was abolished by truncation of the cytoplasmic domain. Neither amiloride nor ATP exerts its effects by altering the aggregation state of the receptor, Comparison of the measured number of ANF binding sites with immunoassayable receptor protein revealed that the stoichiometry of ANF binding to the R1 receptor was 1:2. This was confirmed by using an ANF analog that bears a photoactivatable group at both of its ends, showing that ANF, as for the growth %%%hormone%%%/%%%receptor%%% %%%complex%%%, interacts with both the receptor subunits and specifically cross-links a dimeric form of the receptor, The potential pharmacological consequences of this 1:2 stoichiometric ratio of the ANF-receptor complex are discussed.

14/3,AB/18 (Item 5 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
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11237785 Genuine Article#: GT377 Number of References: 36 Title: CHROMATIN STRUCTURE OF HORMONO-DEPENDENT PROMOTERS
Author(s): ADOM J; CARR KD; GOUILLEUX F; MARSAUD V; RICHARDFOX H Corporate Source: HOP KREMLIN BICETRE,INSERM,U33,UNITE RECH COMMUN HORMONALES,78 AVE GEN LECLERC/F-94275 LE KREMLIN BICETR//FRANCE/; HOP KREMLIN BICETRE,INSERM,U33,UNITE RECH COMMUN HORMONALES,78 AVE GEN LECLERC/F-94275 LE KREMLIN BICETR//FRANCE/
Journal: JOURNAL OF STEROID BIOCHEMISTRY AND MOLECULAR BIOLOGY, 1991, V40, N1-3, P325-332
Language: ENGLISH Document Type: ARTICLE
Abstract: Transient transfections of mutated MMTV LTRs, driving the luciferase reporter gene, have shown the presence of at least one cis-acting element cooperating with the GREs. Studies of the chromatin structure of two glucocorticoid-regulated promoters, the mouse mammary tumor virus (MMTV) long terminal repeat (LTR), a retroviral promoter, and the rat tyrosine aminotransferase (TAT) promoter, demonstrate that both DNAs are organized into precisely positioned nucleosomes. Hormonal activation of transcription is accompanied by structural changes of one (MMTV LTR) or two (TAT promoter) nucleosomes associated with the hormone-response elements (HREs). These changes can be visualized by the appearance of DNaseI hypersensitive sites. Association of the %%%hormone%%%-%%%receptor%%% %%%complex%%% with the nucleus is necessary to induce the DNaseI hypersensitive site and to maintain transcription, but is not necessary to maintain DNaseI hypersensitivity. Anti-hormones, even when able to promote a strong binding

of the receptor to the nucleus, are unable to induce the chromatin structural change. Using cell lines containing approx. 200 copies of a MMTV LTR/(H)v-ras %%%chimeric%%% construct, we have demonstrated a strong, hormono-independent nuclear matrix interaction of sequences located just upstream and downstream of the ras coding sequences.

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 $104.10  Estimated total session cost   0.206 Hrs.

File 155:MEDLINE(R)  1966-1998/Jun W4
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274 S1
141 S2
S3 3 S1 AND S2
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3/3,AB/1
DIALOG(R)File 155:MEDLINE(R)
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08970919 97179056
hCG-receptor binding and transmembrane signaling.
Puett D; Bhowmick N; Fernandez LM; Huang J; %%%Wu C%%%; %%%Narayan P%%% Department of Biochemistry and Molecular Biology, University of Georgia, Athens 30602, USA. puett@bchiris.biochem.uga.edu
Mol Cell Endocrinol (IRELAND) Dec 20 1996, 125 (1-2) p55-64, ISSN 0303-7207 Journal Code: E69
Contract/Grant No.: DK33973, DK, NIDDK
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL The technique of site-directed mutagenesis has proven to be quite powerful in elucidating contact sites involved in the interaction of the heterodimeric glycoprotein hormones and their respective seven transmembrane (TM) G protein-coupled receptors. Our laboratory has focused on identification of the minimum core sequences of the alpha and beta subunits required for bioactivity, the minimum length of a conjoined (yoked) single-chain hCG, the amino acid residues on hCG and the LH/CG-receptor (LH/CG-R) responsible for high-affinity binding, and the regions of the receptor that are involved in TM signaling. A number of amino acid residues have been mapped on the alpha and beta subunits of hCG that appear important in receptor binding. When projected onto the crystal structure of HF-treated hCG, these residues, by and large, cluster on one side of the molecule and cover a sizeable surface area, indicating that the hormone-receptor binding interface is rather extensive. Based on mutagenesis studies of several conserved ionizable amino acid residues in the extracellular domain (ECD) of LH/CG-R and a model that we, in collaboration with Drs Lapthorn and Isaacs, have developed for this region based on the crystal structure of porcine ribonuclease inhibitor, a charged region that appears to play an important role in hormone-receptor recognition has been identified. We have also delineated several regions of LH/CG-R that do not appear to participate in hCG binding but are involved in hCG-mediated signaling. These regions are located in the ECD and extracellular loop III just prior to entry into the membrane via TM helices I and VII, respectively, and in TM helices VI and VII. Similarly, a homologous region in the ECD of the FSH receptor, located with ten residues of TM helix I, is important in signaling but not hormone binding. These results suggest that ligand binding and ligand-mediated receptor activation are quasi-distinct, albeit sequential phenomena. Collectively, our mutagenesis and modeling studies, coupled with results from other laboratories, argue for a ligand-induced conformational change of the receptor that may involve a relative reorientation of the TM helices.

3/3,AB/2
DIALOG(R)File 155:MEDLINE(R)
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08830541 97094949
Protein engineering of a novel constitutively active hormone-receptor complex.
%%%Wu C%%%; %%%Narayan P%%%; Puett D
Department of Biochemistry and Molecular Biology, University of Georgia, Athens, Georgia 30602-7229, USA.
J Biol Chem (UNITED STATES) Dec 6 1996, 271 (49) p31638-42, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: DK-33973, DK, NIDDK
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Human chorionic gonadotropin (hCG) is a heterodimeric glycoprotein hormone consisting of an alpha and a beta subunit that stimulates intracellular levels of cAMP via a G protein-coupled receptor. Herein we report the engineering and characterization of a novel molecule in which the receptor and its heterodimeric ligand were covalently linked in a single polypeptide chain. The hormone-receptor complex was expressed in cells transfected with this construct, but the cells were unable to bind significant amounts of exogenous hCG. However, cleavage of the hormone with a site-specific protease rendered the receptor accessible to exogenously added hormone. Cells transfected with the hCG-receptor construct contained elevated basal levels of cAMP; moreover, addition of hormone had no significant effect. These results are consistent with a strong and stable interaction between the single-chain hormone and its covalently linked receptor that results in a constitutively active complex.

3/3,AB/3
DIALOG(R)File 155:MEDLINE(R)
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08568392 96192928
Functional expression of yoked human chorionic gonadotropin in baculovirus-infected insect cells.
%%%Narayan P%%%; %%%Wu C%%%; Puett D
Department of Biochemistry and Molecular Biology, University of Georgia, Athens 30602, USA.
Mol Endocrinol (UNITED STATES) Dec 1995, 9 (12) p1720-6, ISSN 0888-8809 Journal Code: NGZ
Contract/Grant No.: DK-33973, DK, NIDDK
Languages: ENGLISH
Document type: JOURNAL ARTICLE
hCG is a glycoprotein hormone composed of an alpha-subunit, common to all gonadotropins and to TSH, and a hormone-specific beta-subunit. The non-covalent association of the two subunits is an obligatory step for the formation of biologically active hormones. The correct assembly of the heterodimer is also important for efficient secretion of the hormone, receptor binding, and signal transduction. Herein, we have demonstrated that expression of the two subunits from independent promoters present in a single recombinant baculovirus resulted in subunit association and secretion of biologically active holoprotein by the insect cells. To determine whether the active conformation of heterodimer could be achieved when the two subunits were synthesized in tandem on a single polypeptide chain, two single chain or yoked hCG1, the C-terminus of the complete beta-subunit (145 amino acid residues) was conjoined to the N-terminus of the alpha-subunit. Yoked hCG2 was similar, except that it contained the N-terminal 123 amino acid residues of the beta-subunit. Both yoked hCG molecules bound LH/CG receptor with high affinity and stimulated adenylate cyclase and progesterone levels in transformed mouse Leydig (MA-10) cells. Therefore, the alpha- and beta-subunits are able to fold into a biologically active conformation when covalently linked. Interestingly, when compared with urinary hCG, the hormone expressed in baculovirus-infected insect cells binds to the LH/CG receptor with higher affinity, but exhibits diminished signaling, thus providing another example of a partial

dissociation between receptor binding and activation. ? e au=campbell r

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8/3,AB/1
DIALOG(R)File 155:MEDLINE(R)
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07686867 94068417
Production and fluorescence-activated cell sorting of Escherichia coli expressing a functional antibody fragment on the external surface. Francisco JA; %%%Campbell R%%%; Iverson BL; Georgiou G
Department of Chemical Engineering, University of Texas, Austin 78712. Proc Natl Acad Sci U S A (UNITED STATES) Nov 15 1993, 90 (22) p10444-8 , ISSN 0027-8424 Journal Code: PV3
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We have expressed a single chain Fv (scFv) antibody fragment, consisting of the variable heavy and variable light domains from two separate anti-digoxin monoclonal antibodies, on the external surface of Escherichia coli by fusing it to an Lpp-OmpA %%%hybrid%%% previously shown to direct heterologous proteins to the cell surface. This scFv fusion was expressed at a high level and was shown to bind the hapten with high affinity and specificity. Whole cell ELISAs, fluorescence microscopy, protease sensitivity, and flow cytometry all confirmed that the scFv was anchored on the outer membrane and was accessible on the surface.

Utilizing fluorescence-activated cell sorting, we were able to specifically enrich scFv-producing cells from a 10(5)-fold excess of control cells in only two steps. The expression of antibody fragments on the surface of E. coli is being evaluated as an attractive method for the in vitro production and selection of useful antibody fragments.

8/3,AB/2
DIALOG(R)File 155:MEDLINE(R)
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03857450 82215176
Effects of immunoglobulin structure on Fc receptor binding: a mouse myeloma variant immunoglobulin with a gamma 2b-gamma 2a %%%hybrid%%% heavy chain having a complete gamma 2a Fc region fails to bind to gamma 2a Fc receptors on mouse macrophages.
Birshtein BK; %%%Campbell R%%%; Diamond B
J Immunol (UNITED STATES) Aug 1982, 129 (2) p610-4, ISSN 0022-1767 Journal Code: IFB
Contract/Grant No.: AI 12509, AI, NIAID; AI 10702, AI, NIAID; 16166 Languages: ENGLISH
Document type: JOURNAL ARTICLE
We report here the primary structure of an immunoglobulin heavy chain synthesized by ICR 16, a variant of the MPC 11 mouse myeloma cell line. The ICR 16 heavy chain is a gamma 2b-gamma 2a %%%hybrid%%%, consisting of the CH1 domain of gamma 2b and the hinge, CH2 and CH3 domains of gamma 2a subclasses. The genetic mechanism by which ICR 16 occurred may be recombination, based on homologies in both coding and intervening sequences in gamma 2b and gamma 2a constant region genes. Although the Fc fragment of ICR 16 is completely gamma 2a-like and has been shown to bind to gamma 2a Fc receptors on mouse macrophages, the intact H2L2 molecules is unable to do so. Such an observation underscores the crucial role that conformation may play in the ability of immunoglobulins to carry out biologic functions.

8/3,AB/3
DIALOG(R)File 155:MEDLINE(R)
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03823618 80198307
A gamma 2b-gamma 2a %%%hybrid%%% immunoglobulin heavy chain produced by a variant of the MPC 11 mouse myeloma cell line.
Birshtein BK; %%%Campbell R%%%; Greenberg ML
Biochemistry (UNITED STATES) Apr 29 1980, 19 (9) p1730-7, ISSN 0006-2960 Journal Code: A0G
Languages: ENGLISH
Document type: JOURNAL ARTICLE
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DIALOG(R)File 155:MEDLINE(R)
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09097760 97278315
%%%Chimeric%%% proteins can exceed the sum of their parts: implications for evolution and protein design.
%%%Campbell RK%%%; Bergert ER; Wang Y; Morris JC; Moyle WR Department of OBGYN, Robert Wood Johnson (Rutgers) Medical School, Piscataway, NJ 08854, USA.
Nat Biotechnol (UNITED STATES) May 1997, 15 (5) p439-43, ISSN 1087-0156 Journal Code: CQ3
Contract/Grant No.: HD14907, HD, NICHD; HD15454, HD, NICHD; DK42008, DK, NIDDK
Languages: ENGLISH
Document type: JOURNAL ARTICLE
%%%Chimeric%%% analogs derived from pairs of homologous proteins routinely exhibit activities found in one or both parents. We describe %%%chimeras%%% of two glycoprotein hormones, human chorionic gonadotropin (hCG) and human follitropin (hFSH), that exhibit activity unique to a third family member, human thyrotropin (hTSH). The results show that biological activity can be separated from hormone-specific amino acid residues. This is consistent with a model for the evolution of homologous ligand-receptor pairs involving gene duplication and the creation of inhibitory determinants that restrict binding. Disruption of these determinants can unmask activities characteristic of other members of a protein family. Combining portions of two ligands to create analogs with properties of a third family member can facilitate identifying key determinants of protein-protein interaction and may be a useful strategy for creating novel therapeutics. In the case of the glycoprotein hormones, this showed that two different hormone regions (i.e., the seat-belt and the intersubunit groove) appear to limit inappropriate contacts with receptors for other members of this family. These observations also have important caveats for %%%chimera%%% -based protein design because an unexpected gain of function may limit the therapeutic usefulness of some %%%chimeras%%%.

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08953900 97166171
Influence of subunit interactions on lutropin specificity. Implications for studies of glycoprotein hormone function.
Cosowsky L; Lin W; Han Y; Bernard MP; %%%Campbell RK%%%; Moyle WR Department of Obstetrics and Gynecology, Robert Wood Johnson (Rutgers) Medical School, Piscataway, New Jersey 08854, USA.
J Biol Chem (UNITED STATES) Feb 7 1997, 272 (6) p3309-14, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: HD14907, HD, NICHD; HD15454, HD, NICHD Languages: ENGLISH
Document type: JOURNAL ARTICLE
Bovine lutropin (bLH) and human chorionic gonadotropin

(hCG) are heterodimeric glycoprotein hormones required for reproduction. Both bind rat LH receptors (rLHRs), but hCG binds human LH receptors (hLHRs) 1000-10,000 fold better than bLH. We tested the premise that this difference in affinity could be used to identify lutropin receptor contacts. Heterodimers containing hCG/bLH alpha- or beta-subunit %%%chimeras%%% that bound hLHR like hCG (or bLH) were expected to have hCG (or bLH) residues at the receptor contact sites. Analogs containing one subunit derived from hCG bound hLHR much more like hCG than bLH, indicating that each bLH subunit contains all the residues sufficient for high affinity hLHR binding. Indeed, the presence of bovine alpha-subunit residues increased the activities of some hCG analogs. The low hLHR activity of bLH was due primarily to an interaction between its alpha-subunit and beta-subunit residue Leu95. Leu95 does not appear to contact the hLHR since it did not influence the hLHR activity of heterodimers containing human alpha-subunit. These observations show that interactions within and between the subunits can significantly influence the activities of lutropins, thereby confounding efforts to identify ligand residues that contact these receptors.

10/3,AB/3
DIALOG(R)File 155:MEDLINE(R)
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08616483 96281915
HLA-DR4-IE %%%chimeric%%% class II transgenic, murine class II-deficient mice are susceptible to experimental allergic encephalomyelitis. Ito K; Bian HJ; Molina M; Han J; Magram J; Saar E; Belunis C; Bolin DR; Arceo R; %%%Campbell R%%%; Falcioni F; Vidovic D; Hammer J; Nagy ZA Department of Inflammation and Autoimmune Diseases, Hoffmann-La Roche Inc., Nutley, New Jersey 07110, USA.
J Exp Med (UNITED STATES) Jun 1 1996, 183 (6) p2635-44, ISSN 0022-1007 Journal Code: I2V
Languages: ENGLISH
Document type: JOURNAL ARTICLE
To investigate the development of HLA-DR-associated autoimmune diseases, we generated transgenic (Tg) mice with HLA-DRA-IE alpha and HLA-DRB1*0401-IE beta %%%chimeric%%% genes. The transgene-encoded proteins consisted of antigen-binding domains from HLA-DRA and HLA-DRB1*0401 molecules and the remaining domains from the IE(d)-alpha and IE(d)-beta chains. The %%%chimeric%%% molecules showed the same antigen-binding specificity as HLA-DRB1*0401 molecules, and were functional in presenting antigens to T cells. The Tg mice were backcrossed to MHC class II-deficient (IA beta-, IE alpha-) mice to eliminate any effect of endogenous MHC class II genes on the development of autoimmune diseases. As expected, IA alpha beta or IE alpha beta molecules were not expressed in Tg mice. Moreover, cell-surface expression of endogenous IE beta associated with HLA-DRA-IE alpha was not detectable in several Tg mouse lines by flow cytometric analysis. The HLA-DRA-IE alpha/HLA-DRB1*0401-IE beta molecules rescued the development of CD4+ T cells in MHC class II-deficient mice, but T cells expressing V beta 5, V beta 11, and V beta 12 were specifically deleted. Tg mice were immunized with peptides, myelin basic protein (MBP) 87-106 and proteolipid protein (PLP) 175-192, that are considered to be immunodominant epitopes in HLA-DR4 individuals. PLP175-192 provoked a strong proliferative response of lymph node T cells from Tg mice, and caused inflammatory lesions in white matter of the CNS and symptoms of experimental allergic encephalomyelitis (EAE). Immunization with MBP87-106 elicited a very weak proliferative T cell response and caused mild EAE. Non-Tg mice immunized with either PLP175-192 or MBP87-106 did not develop EAE. These results demonstrated that a human MHC class II binding site alone can confer susceptibility to an experimentally induced murine autoimmune disease.

10/3,AB/4
DIALOG(R)File 155:MEDLINE(R)
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08386568 95378256
Model of human chorionic gonadotropin and lutropin receptor interaction that explains signal transduction of the glycoprotein hormones. Moyle WR; %%%Campbell RK%%%; Rao SN; Ayad NG; Bernard MP; Han Y; Wang Y Department of Obstetrics/Gynecology, Robert Wood Johnson (Rutgers) Medical School, Piscataway, New Jersey 08854, USA.
J Biol Chem (UNITED STATES) Aug 25 1995, 270 (34) p20020-31, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: HD14907, HD, NICHD; HD24650, HD, NICHD; HD15454, HD, NICHD
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The goal of these studies was to devise a model that explains how human chorionic gonadotropin (hCG) interacts with lutropin (LH) receptors to elicit a hormone signal. Here we show that alpha-subunit residues near the N terminus, the exposed surface of the cysteine knot, and portions of the first and third loops most distant from the beta-subunit interface were recognized by antibodies that bound to hCG-receptor complexes. These observations were combined with similar data obtained for the beta-subunit (Cosowsky, L., Rao, S.N.V., Macdonald, G.J., Papkoff, H., Campbell, R.K., and Moyle, W.R. (1995) J. Biol. Chem. 270, 20011-20019), information on residues of hCG that can be changed without disrupting hormone function, the crystal structure of deglycosylated hCG, and the crystal structure of a leucine-repeat protein to devise a model of hCG-receptor interaction. This model suggest that the extracellular domain of the LH receptor is "U-" or "J"-shaped and makes several contacts with the transmembrane domain. High affinity hormone binding results from interactions between residues in the curved portion of the extracellular domain of the receptor and the groove in the hormone formed by the apposition of the second alpha-subunit loop and the first and third beta-subunit loops. Most of the remainder of the hormone is found in the large space between the arms of the extracellular domain and makes few, if any, additional specific contacts with the receptor needed for high affinity binding. Signal transduction is caused by steric or other influences of the hormone on the distance between the arms of the extracellular domain, an effect augmented by the oligosaccharides. Because the extracellular domain is coupled at multiple sites to the transmembrane domain, the change in conformation of the extracellular domain is relayed to the transmembrane domain and subsequently to the cytoplasmic surface of the plasma membrane. While the model does not require the hormone to contact the transmembrane domain to initiate signal transduction, small portions of both subunits may be near the transmembrane domain and assist in initiating the hormonal signal. This is the first model that is consistent with all known information on the activity of the gonadotropins including the amounts of the hormone that are exposed in the hormone-receptor complex, the apparent lack of specific contacts between much of the hormone and the receptor, and the roles of the oligosaccharides in signal transduction.(ABSTRACT TRUNCATED AT 400 WORDS)

10/3,AB/5
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08386567 95378255
The groove between the alpha- and beta-subunits of hormones with lutropin (LH) activity appears to contact the LH receptor, and its conformation is changed during hormone binding.
Cosowsky L; Rao SN; Macdonald GJ; Papkoff H; %%%Campbell RK%%%; Moyle WR Department of Obstetrics/Gynecolgy, Robert Wood Johnson (Rutgers) Medical School, Piscataway, New Jersey 08854, USA.
J Biol Chem (UNITED STATES) Aug 25 1995, 270 (34) p20011-9, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: HD05722, HD, NICHD; HD14907, HD, NICHD; HD24650, HD, NICHD; +
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Gonadotropins are heterodimeric glycoprotein hormones that control vertebrate fertility through their actions on gonadal lutropin (luteinizing hormone, LH) and follitropin (follicle-stimulating hormone, FSH) receptors. The beta-subunits of these hormones control receptor binding specificity; however, the region of the beta-subunit that contacts the receptor has not been identified. By a process of elimination we show this contact to be the portions of beta-subunit loops one and three found in a hormone groove created by the juxtaposition of the alpha- and beta-subunits. Most other regions of the beta-subunit can be recognized by antibodies that bind to human chorionic hormone (hCG)-receptor complexes or replaced without disrupting hormone function. Using a series of bovine LH/hCG and human FSH/hCG beta-subunit %%%chimeras%%% we identified key hCG beta-subunit residues in the epitopes of two antibodies that bind to hCG-receptor complexes. These epitopes include the surfaces of beta-subunit loops one and three near residue 74 on the outside of the hormone groove and parts of the C-terminal end of the "seat belt" that holds the two subunits together. The antibody that recognized residue 74 bound to receptor complexes containing most mammalian lutropins better than to the free hormones, an indication that the outside surface of the beta-subunit groove is altered during hormone binding. This region of the beta-subunit is furthest from the alpha-subunit and is recognized equally well in the free beta-subunit and in the heterodimer. Thus, the receptor associated increase in antibody binding appears due to an interaction of this portion of the beta-subunit with the receptor and not to an effect of the receptor on the relative positions of the alpha- and beta-subunits. Unlike most previous studies designed to identify portions of the beta-subunit likely to contact the LH receptor, this indirect approach provides data that are more easily interpreted because it does not rely on the use of mutations that disrupt hormone function. The approach described here should be valuable for studying the receptor interactions of other complex ligands.

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08014455 95001918
High-affinity, specific factor IXa binding to platelets is mediated in part by residues 3-11.
Ahmad SS; Rawala-Sheikh R; Cheung WF; %%%Jameson BA%%%; Stafford DW; Walsh PN
Sol Sherry Thrombosis Research Center, Department of Biochemistry, Temple University School of Medicine, Philadelphia, Pennsylvania 19140. Biochemistry (UNITED STATES) Oct 11 1994, 33 (40) p12048-55, ISSN 0006-2960 Journal Code: A0G
Contract/Grant No.: HL45486, HL, NHLBI; HL2566, HL, NHLBI; HL46213, HL, NHLBI; +
Languages: ENGLISH
Document type: JOURNAL ARTICLE
To identify the amino acids in the Gla domain that mediate factor IXa binding to human platelets, we have used %%%chimeric%%% molecules and point mutations in the Gla domain of recombinant factor IX, based on molecular modeling using the coordinates of the Gla domain of bovine prothrombin, which reveals two surface structures whose sequences differ among factor IX, factor X, and factor VII. Binding to thrombin-activated platelets of factor IXa in the presence of factor VIIIa (2 units/mL) and factor X (1.5 microM) revealed a stoichiometry of approximately 550 sites per platelet with a Kd of approximately 0.65 nM compared with a Kd of approximately 2.5 nM in the absence of factor VIIIa and factor X. In contrast, mutations of factor IX to factor X residues at positions 4 and 5 or at positions 9, 10, and 11 results in decreases in the number of sites and affinity of factor IXa binding in the presence or absence of factor VIIIa and factor X. A %%%chimera%%% consisting of the Gla domain of factor VII with factor IX residues at positions 33, 34, 35, 39, and 40 displayed abnormal factor IXa binding and a decreased Vmax and a normal Km for factor X activation, and the replacement of amino acid residues 3-10 with those of factor IX restored normal binding and factor X activation kinetics to this %%%chimeric%%% protein.(ABSTRACT TRUNCATED AT 250 WORDS)

10/3,AB/7
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07886010 94195396
Co-evolution of ligand-receptor pairs.
Moyle WR; %%%Campbell RK%%%; Myers RV; Bernard MP; Han Y; Wang X Department of Obstetrics and Gynecology, University of Medicine and Dentistry of New Jersey-Robert Wood Johnson (Rutgers) Medical School, Piscataway 08854.
Nature (ENGLAND) Mar 17 1994, 368 (6468) p251-5, ISSN 0028-0836 Journal Code: NSC
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Specific receptors for lutropin (luteinizing hormone; LH) and follitropin (follicle-stimulating hormone; FSH) mediate the actions of human chorionic gonadotropin (hCG) and FSH5 on the gonads. Here we report that short independent sequences of the beta-subunit enable hCG to distinguish between the receptors for FSH and LH. Residues between the 11th and 12th cysteines restrict FSH receptor binding; residues between the 10th and 11th cysteines and, to a much lesser extent, residues carboxy-terminal to the 12th cysteine also affect LH receptor binding. CF101-109, an hCG analogue containing hFSH beta residues between the 11th and 12th cysteines, had high affinity for both LH and FSH receptors. Modifications to CF101-109 that reduce binding to either LH or FSH receptors yield gonadotropin analogues having differing ratios of LH:FSH activity. Ligand-binding specificity of the LH receptor is determined by residues encoded by parts of exons 2-4 and 7-9 which prevent hFSH binding but have little effect on hCG binding. FSH receptor specificity is controlled primarily by residues encoded by exons 5 and 6 that prevent hCG binding but have little effect on hFSH binding. These determinants can be interchanged to

create receptor analogues that bind hCG and hFSH. Our observations support a model in which distinct negative determinants restrict ligand-receptor interaction. This explains coevolution of binding specificity in families of homologous ligands and their receptors. Natural or designed manipulation of these determinants leads to the 'evolution' of new, specific protein-protein interactions.

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07335869 92192337
Assembly and expression of a synthetic gene encoding the bovine glycoprotein hormone alpha-subunit.
%%%Campbell RK%%%; Erfle H; Barnett RW; Moyle WR
University of Medicine and Dentistry of New Jersey, Robert Wood Johnson (Rutgers) Medical School, Piscataway 08854.
Mol Cell Endocrinol (NETHERLANDS) Feb 1992, 83 (2-3) p195-200, ISSN 0303-7207 Journal Code: E69
Contract/Grant No.: HD14709, HD, NICHD
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The glycoprotein hormones are a family of alpha beta heterodimeric proteins which are responsible for gonadal and thyroid function. In previous studies we employed %%%chimeric%%% glycoprotein hormone beta-subunits to identify amino acid residues critical for binding to receptors and antibodies. To facilitate similar studies of the alpha-subunit of these hormones, we assembled a 406 bp synthetic gene which encodes the human alpha-subunit leader sequence and the secreted portion of the bovine alpha-subunit. It contains unique restriction sites that can be used for cassette mutagenesis or for making human/bovine alpha-subunit %%%chimeras%%% . The gene was assembled from eight long oligodeoxynucleotides in a single ligation and its structure verified by DNA sequencing. Co-transfection of COS-7 cells with the synthetic gene and the cDNA for human chorionic gonadotropin (hCG) beta-subunit resulted in the secretion of a functional alpha beta heterodimer which bound to luteinizing hormone receptors. The protein was recognized by several monoclonal antibodies including B109, an antibody to a conformational epitope which binds hCG but not the free bovine alpha-, human alpha-, or hCG beta-subunits. This suggests that the binding site for B109 may be formed by residues located primarily within the hCG beta-subunit and that formation of this epitope requires a change in conformation of the beta-subunit when it combines with the alpha-subunit.

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06984803 90256768
Localization of residues that confer antibody binding specificity using human chorionic gonadotropin/luteinizing hormone beta subunit %%%chimeras%%% and mutants.
Moyle WR; Matzuk MM; %%%Campbell RK%%%; Cogliani E; Dean-Emig DM; Krichevsky A; Barnett RW; Boime I
Department of Obstetrics/Gynecology, Robert Wood Johnson (Rutgers) Medical School, Piscataway, New Jersey 08854.
J Biol Chem (UNITED STATES) May 25 1990, 265 (15) p8511-8, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: HD14907, HD, NICHD; HD23398, HD, NICHD; HD15454, HD, NICHD; +
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The glycoprotein hormones are a family of conserved heterodimeric proteins which share a common alpha subunit but differ in their hormone-specific beta subunits. We used %%%chimeras%%% of human chorionic gonadotropin (hCG) and luteinizing hormone (hLH) beta subunits to identify residues which enable monoclonal antibodies (mAb) to distinguish the two hormones. The LH beta-CG beta %%%chimeras%%% appeared to fold similar to hCG beta, since they combined with hCG alpha and, depending on their sequences, were recognized by hCG-selective mAbs. Amino acid residues Arg8-Arg10,Gly47-Ala51, and Gln89-Leu92 form a major epitope region and appear to be adjacent to each other on the surface of hCG beta. Gly47-Ala51 and Gln89-Leu92 are recognized by dimer-specific mAbs while Arg8-Arg10 is recognized by mAbs which have highest affinity for the free beta subunit. These observations suggest that the conformation of this region of the beta subunit changes when the alpha and beta subunits combine. Residues which are C-terminal of Asp112 form a second epitope domain. mAbs to the third domain distinguish hCG beta and hLH beta by the presence of Asn77 in hCG beta and can be detected after hCG binds to receptors. These findings were used to develop a model of hCG beta which predicts the locations of these residues and their positions relative to the alpha subunit and receptor interfaces.

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06787620 91126075
Conversion of human choriogonadotropin into a follitropin by protein engineering.
%%%Campbell RK%%%; Dean-Emig DM; Moyle WR
Department of Obstetrics & Gynecology, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Piscataway 08854.
Proc Natl Acad Sci U S A (UNITED STATES) Feb 1 1991, 88 (3) p760-4, ISSN 0027-8424 Journal Code: PV3
Contract/Grant No.: HD14709, HD, NICHD; HD24650, HD, NICHD Languages: ENGLISH
Document type: JOURNAL ARTICLE
Human reproduction is dependent upon the actions of follicle-stimulating hormone (hFSH), luteinizing hormone (hLH), and chorionic gonadotropin (hCG). While the alpha subunits of these heterodimeric proteins can be interchanged without effect on receptor-binding specificity, their beta subunits differ and direct hormone binding to either LH/CG or FSH receptors. Previous studies employing chemical modifications of the hormones, monoclonal antibodies, or synthetic peptides have implicated hCG beta-subunit residues between Cys-38 and Cys-57 and corresponding regions of hLH beta and hFSH beta in receptor recognition and activation. Since the beta subunits of hCG or hLH and hFSH exhibit very little sequence similarity in this region, we postulated that these residues might contribute to hormone specificity. To test this hypothesis we constructed %%%chimeric%%% hCG/hFSH beta subunits, coexpressed them with the human alpha subunit, and examined their ability to interact with LH and FSH receptors and hormone-specific monoclonal antibodies. Surprisingly, substitution of hFSH beta residues 33-52 for hCG beta residues 39-58 had no effect on receptor binding or stimulation. However, substitution of hFSH beta residues 88-108 in place of the carboxyl terminus of hCG beta

(residues 94-145) resulted in a hormone analog identical to hFSH in its ability to bind and stimulate FSH receptors. The altered binding specificity displayed by this analog is not attributable solely to the replacement of hCG beta residues 108-145 or substitution of residues in the "determinant loop" located between hCG beta residues 93 and 100.

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04889859 86159371
The lateralization of lip-read sounds: a first look.
%%%Campbell R%%%
Brain Cogn (UNITED STATES) Jan 1986, 5 (1) p1-21, ISSN 0278-2626 Journal Code: AM9
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Two tachistoscopic studies on the lateralization of lip-read still photographs in normal right handers are reported. In the first, subjects matched a still lip photograph with a heard speech sound. A clear right hemisphere (LVF) advantage emerged, despite the phonological requirements of this task. This pattern of laterality failed to interact with the type of response (same/different) or with the status of the heard phoneme; both consonant and vowel matching showed the same pattern of LVF advantage, despite the significantly greater difficulty of consonant than vowel matching in this particular task. In the second study subjects were required to speak the sound they saw being spoken by a centrally displayed face photograph. The displayed face was %%%chimeric%%%; that is, one side of the face was seen saying one sound, one side another. Here, a rather complex pattern of results ensued. For the speakers seen a clear expressor asymmetry emerged; speech sounds were judged more accurately when they issued from the right side of the speaker's face. However, in the LVF, and only the LFV, accuracy in reporting %%%chimeric%%% face sounds correlated with speed in learning to lip-read, suggesting that the LVF is systematically involved even when task demands (speaking the response, phonological analysis, small, more central displays) do not, at first sight, suggest that they should. Taken together, these studies suggest that the right hemisphere could support some aspects of the processing of seen speech in normally hearing, normally lateralized individuals. ? s s7 and fusion not (s8 or s9)

387 S7
61744 FUSION
3 S8
11 S9
S11 11 S7 AND FUSION NOT (S8 OR S9)
? t s11/3,ab/all

11/3,AB/1
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08680708 96113548
Expression of Trichoderma reesei and Trichoderma viride xylanases in Escherichia coli.
Sung WL; Luk CK; Chan B; Wakarchuk W; Yaguchi M; %%%Campbell R%%%; Willick G; Ishikawa K; Zahab DM
Institute for Biological Sciences, National Research Council of Canada, Ottawa, ON, Canada.
Biochem Cell Biol (CANADA) May-Jun 1995, 73 (5-6) p253-9, ISSN 0829-8211 Journal Code: ALR
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Synthetic genes encoding the 190 amino acid Trichoderma reesei xylanase II (TrX) and the closely related Trichoderma viride xylanases have been synthesized in a two-step procedure. Initially, a partial gene encoding amino acids 92-190 was constructed in %%%fusion%%% with the N-terminal half of the Bacillus circulans xylanase (BcX). The remaining BcX gene sequence was replaced during the assembly of the coding sequence for amino acids 1-91. Expression of the synthetic genes in Escherichia coli yielded recombinant xylanases with specific activity generally identical with the natural TrX. However, the recombinant TrX showed thermostability and temperature optimum lower than those of the natural TrX, thus indicating that the posttranslational modifications of the latter in its fungal host are essential to its greater stability. A mutation N19K further decreased the thermostability of the recombinant TrX.

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08578615 96212188
Thrombin-induced platelet aggregation is inhibited by the heptapeptide Leu271-Ala277 of domain 3 in the heavy chain of high molecular weight kininogen.
Kunapuli SP; Bradford HN; %%%Jameson BA%%%; DeLa Cadena RA; Rick L; Wassell RP; Colman RW
Sol Sherry Thrombosis Research Center, Temple University School of Medicine, Philadelphia, Pennsylvania 19140, USA.
J Biol Chem (UNITED STATES) May 10 1996, 271 (19) p11228-35, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: HL45486, HL, NHLBI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The ability of kininogens to modulate thrombin-induced aggregation of human platelets has been assigned to domain 3 (D3) in the common heavy chain coded for by exons 7, 8, and 9 of kininogen gene. We expressed each of the exons 7, 8, and 9, and various combinations as glutathione S-transferase %%%fusion%%% proteins in Escherichia coli. Each of the exon products 7 (Lys236-Gln292), 9 (Val293-Gly328), and 8 (Gln329-Met357), and their combinations were evaluated for the ability to inhibit thrombin induced platelet aggregation. Only products containing exon 7 inhibited platelet aggregation induced by thrombin with an IC50 of > 20 microM. A deletion mutant of exon 7 product, polypeptide 7A product (Lys236-Lys270) did not block thrombin-induced platelet aggregation, while 7B product (Thr255-Gln292) and 7C product (Leu271-Gln292) inhibited aggregation. These findings indicated that the inhibitory activity is localized to residues Leu271-Gln292. Peptides Phe279-Ile283 and Phe281-Gln292 did not block thrombin, and Asn275-Phe279 had only minimal inhibitory activity. A heptapeptide Leu271-Ala277 inhibited thrombin-induced aggregation of platelets with an IC50 of 65 microM. The effect is specific for the activation of platelets by thrombin but not ADP or collagen. No evidence for a thrombin-kininogen complex was found, and neither HK nor its derivatives directly inhibited thrombin activity. Knowledge of the critical sequence of kininogen should allow design of compounds that can modulate thrombin activation of platelets.

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08517975 96141064
Rapid and efficient selection of human hematopoietic cells expressing murine heat-stable antigen as an indicator of retroviral-mediated gene transfer.
Conneally E; Bardy P; Eaves CJ; Thomas T; %%%Chappel S%%%; Shpall EJ; Humphries RK
Terry Fox Laboratory, B.C. Cancer Agency, Vancouver, Canada. Blood (UNITED STATES) Jan 15 1996, 87 (2) p456-64, ISSN 0006-4971 Journal Code: A8G
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Recombinant retroviruses offer many advantages for the genetic modification of human hematopoietic cells, although their use in clinical protocols has thus far given disappointing results. There is therefore an important need to develop new strategies that will allow effectively transduced primitive hematopoietic target populations to be both rapidly characterized and isolated free of residual nontransduced but biologically equivalent cells. To address this need, we constructed a murine stem cell virus (MSCV)-based retroviral vector containing the 228-bp coding sequence of the murine heat-stable antigen (HSA) and generated helper virus-free amphotropic MSCV-HSA producer cells by transfection of GP-env AM12 packaging cells. Light density and, in some cases, lineage marker-negative (lin-) normal human marrow or mobilized peripheral blood cells preactivated by exposure to interleukin-3 (IL-3), IL-6, and Steel factor in vitro for 48 hours were then infected by cocultivation with these MSCV-HSA producer cells for a further 48 hours in the presence of the same cytokines. Fluorescence-activated cell sorting (FACS) analysis of the cells 24 hours later showed 21% to 41% (mean, 27%) of those that were still CD34+ to have acquired the ability to express HSA. The extent of gene transfer to erythroid and granulopoietic progenitors (burst-forming unit-erythroid and colony-forming unit-granulocyte-macrophage), as assessed by the ability of these cells to form colonies of mature progeny in the presence of normally toxic concentrations of G418, averaged 11% and 12%, respectively, in 6 experiments. These values could be increased to 100% and 77%, respectively, by prior isolation of the CD34+HSA+ cell fraction and were correspondingly decreased to an average of 2% and 5%, respectively, in the CD34+HSA- cells. In addition, the extent of gene transfer to long-term culture-initiating cells (LTC-IC) was assessed by G418 resistance. The average gene transfer to LTC-IC-derived colony-forming cells in the unsorted population was < or = 7% in 4 experiments. FACS selection of the initially CD34+HSA+ cells increased this value to 86% and decreased it to 3% for the LTC-IC plated from the CD34+HSA- cells. Transfer of HSA gene expression to a phenotypically defined more primitive subpopulation of CD34+ cells, ie, those expressing little or no CD38, could also be shown by FACS analysis of infected populations 24 hours after infection. These findings underscore the potential use of retroviral vectors encoding HSA for the specific identification and non-toxic selection immediately after infection of retrovirally transduced populations of primitive human hematopoietic cells. In addition, such vectors should facilitate the subsequent tracking of their marked progeny using multiparameter flow cytometry.

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08452268 96059350
Heterozygosity at the b mating-type locus attenuates %%%fusion%%% in Ustilago maydis.
Laity C; Giasson L; %%%Campbell R%%%; Kronstad J
Biotechnology Laboratory, University of British Columbia, Vancouver, Canada.
Curr Genet (UNITED STATES) Apr 1995, 27 (5) p451-9, ISSN 0172-8083 Journal Code: CUG
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Mating and pathogenesis of the corn smut fungus, Ustilago maydis, are controlled by two unlinked mating-type loci, a and b. Yeast-like haploids that differ at both loci are compatible and fuse to establish a pathogenic dikaryon. Mating is assayed in vitro by co-inoculation on culture medium containing activated charcoal; compatible combinations have a characteristic "fuzzy" appearance caused by the growth of aerial hyphae. In general, this test has not been useful for assaying the mating ability of strains that are already mycelial (e.g., those heterozygous at b or at both mating-type loci). Using an assay for cytoduction involving transfer of a mitochondrial marker during transient cell %%%fusion%%%, and engineered strains with defined genotypes, we examined the mating abilities of strains heterozygous or hemizygous at the mating-type loci. The data (which have not been available from conventional pathogenicity or plate mating tests) show that heterozygosity at b attenuates %%%fusion%%% in haploid and diploid strains, whereas strains heterozygous at a retain the ability to fuse with a compatible haploid partner. It appears, therefore, that subsequent %%%fusion%%% events are attenuated once %%%fusion%%% has occurred to establish the U. maydis dikaryon.

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07779954 94112125
Towards a structure of the HIV-1 envelope glycoprotein gp120: an immunochemical approach.
Moore JP; %%%Jameson BA%%%; Sattentau QJ; Willey R; Sodroski J Aaron Diamond AIDS Research Center, New York University School of Medicine, New York 10016.
Philos Trans R Soc Lond B Biol Sci (ENGLAND) Oct 29 1993, 342 (1299) p83-8, ISSN 0962-8436 Journal Code: P5Z
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The HIV-1 surface glycoprotein gp120 binds CD4 in the initial state of virus-cell %%%fusion%%%. The extensive glycosylation of gp120 has thus far precluded definition of its structure by crystallographic methods. As an initial approach to a gp120 structure, the surface topology was mapped using antibodies. First, the regions of gp120 that are accessible on the surface of the native molecule, and those that are internal but exposed after denaturation, are identified. Second, epitopes for antibodies that recognize complex surface structures comprising segments of different domains are identified. Third, we define how mutations in one domain of gp120 influence the binding of antibodies to defined epitopes on other domains. These latter approaches enable us to start to understand the inter-domain interactions that contribute to the overall structure of the gp120 molecule. Information from these studies is being used to model the structures of individual gp120 domains, and the way in which these interact in the folded protein.

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07274543 93246012
The cloning of the human follicle stimulating hormone receptor and its expression in COS-7, CHO, and Y-1 cells.
Kelton CA; Cheng SV; Nugent NP; Schweickhardt RL; Rosenthal JL; Overton SA; Wands GD; Kuzeja JB; Luchette CA; %%%Chappel SC%%%
Ares Advanced Technology, Inc., Randolph, MA 02368.
Mol Cell Endocrinol (NETHERLANDS) Nov 1992, 89 (1-2) p141-51, ISSN 0303-7207 Journal Code: E69
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Follicle stimulating hormone (FSH) receptor clones were isolated from a human testis cDNA library. Characterization of the cDNA clones showed that the DNA and predicted amino acid sequences of the long open reading frame differed from a previously published human ovarian FSH receptor sequence (Minegish et al. (1991) Biochem. Biophys. Res. Commun. 175, 1125-1130) by seven nucleotides and five amino acids. A human FSH receptor splice variant was also identified and characterized. A full-length human FSH receptor cDNA was engineered for expression in COS-7, CHO, and Y-1 cells. In transient transfections of COS-7 cells and stable transfections of Y-1 cells, efficient FSH receptor mRNA accumulation and isolation of FSH-responsive cell lines occurred only when an intron was included in the 5' untranslated region of the FSH receptor transcription unit. Y-1 cells stably transfected with the FSH receptor responded to FSH treatment by rounding up and by synthesizing increased amounts of progesterone. Stably transfected CHO cell lines, which responded to FSH by synthesizing increased amounts of cAMP, were isolated irrespective of the presence of the heterologous intron. The FSH-responsive CHO and Y-1 cell lines may be suitable for the development of better in vitro FSH bioassays. These cells also constitute a convenient source of human FSH receptor protein for use in radioreceptor assays and in studies of receptor-ligand interactions.

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07226372 93090475
Conserved structural features in the interaction between retroviral surface and transmembrane glycoproteins?
Schulz TF; %%%Jameson BA%%%; Lopalco L; Siccardi AG; Weiss RA; Moore JP Chester Beatty Laboratories, Institute of Cancer Research, London, England.
AIDS Res Hum Retroviruses (UNITED STATES) Sep 1992, 8 (9) p1571-80, ISSN 0889-2229 Journal Code: ART
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Among the retroviruses, the surface (SU) and transmembrane (TM) glycoproteins of lentiviruses are linked exclusively by noncovalent bonds. For some C-type retroviruses, however, a small proportion of the SU proteins has been shown to be linked to their TM proteins by a disulfide bond, with the remainder being noncovalently associated. A region near the carboxyl terminus of the HIV-1 SU glycoprotein has been implicated in contacting the TM glycoprotein. Computer modelling indicates that this region of divergent lentivirus and oncovirus SU glycoproteins forms a structurally conserved "pocket" which could accommodate a "knob"-like protrusion formed by an immunodominant region in the TM protein containing the CxxxxxC (lentiviruses) or CxxxxxCC (C- and D-type viruses) motif. An anti-idiotypic monoclonal antibody, raised against a monoclonal antibody reacting with a sequence in the "pocket" of HIV-1 gp120, was found to bind to synthetic peptides close to the CxxxxxC motif. It is suggested that part of the SU-TM linkage mechanism for the lentiviruses and oncoviruses is a 'knob and socket' structure and that the interaction between SU and TM proteins is similar in one region for lentiviruses and C-type as well as D-type viruses. The conserved knob and socket linkage may be relevant to a mechanism for viral-cell membrane %%%fusion%%% that is broadly common to all of these retroviruses.

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06992067 91061959
Neuropsychological studies of auditory-visual %%%fusion%%% illusions. Four case studies and their implications.
%%%Campbell R%%%; Garwood J; Franklin S; Howard D; Landis T; Regard M University of Oxford, U.K.
Neuropsychologia (ENGLAND) 1990, 28 (8) p787-802, ISSN 0028-3932 Journal Code: NZN
Languages: ENGLISH
Document type: JOURNAL ARTICLE
A heard speech sound which is not the same as the synchronized speech sound can sometimes give rise to an illusory phonological percept. Typically, a heard /ba/ combines with a seen /ga/ to give the impression that /da/ has been heard (McGurk, H. and MacDonald, J. Nature Lond. 264, 746-748, 1976). We report the susceptibility to this illusion of four individuals with localized brain lesions affecting perceptual function. We compare their performance to that of ten control subjects and relate these findings to the efficiency of processing seen and heard speech in separate and combined modalities. The pattern of performance strongly suggests LH specialization for the phonological integration of seen and heard speech. The putative site of such integration can be effectively isolated from unilateral and from bilateral inputs and may be driven by either modality.

11/3,AB/9
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06011820 88300908
Identification of a novel retroviral gene unique to human immunodeficiency virus type 2 and simian immunodeficiency virus SIVMAC. Kappes JC; Morrow CD; Lee SW; %%%Jameson BA%%%; Kent SB; Hood LE; Shaw GM ; Hahn BH
Department of Medicine, University of Alabama, Birmingham 35294. J Virol (UNITED STATES) Sep 1988, 62 (9) p3501-5, ISSN 0022-538X Journal Code: KCV
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Human and simian immunodeficiency-associated retroviruses are extraordinarily complex, containing at least five genes, tat, art, sor, R, and 3' orf, in addition to the structural genes gag, pol, and env. Recently, nucleotide sequence analysis of human immunodeficiency virus type 2 (HIV-2) and simian immunodeficiency virus SIVMAC revealed the existence of still another open reading frame, termed X, which is highly conserved between these two viruses but absent from HIV-1. In this report, we demonstrate for the first time that the X open reading frame represents a functional retroviral gene in both HIV-2 and SIVMAC and that it encodes a virion-associated protein of 14 and 12 kilodaltons, respectively. We also describe the production of recombinant TrpE/X %%%fusion%%% proteins in Escherichia coli and show that sera from some HIV-2-infected individuals

specifically recognize these proteins.

11/3,AB/10
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05888398 88235916
Location and chemical synthesis of a binding site for HIV-1 on the CD4 protein.
%%%Jameson BA%%%; Rao PE; Kong LI; Hahn BH; Shaw GM; Hood LE; Kent SB Division of Biology, California Institute of Technology, Pasadena 91125. Science (UNITED STATES) Jun 3 1988, 240 (4857) p1335-9, ISSN 0036-8075 Journal Code: UJ7
Contract/Grant No.: AI25784, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The human immunodeficiency virus type 1 (HIV-1) uses the CD4 protein as a receptor for infection of susceptible cells. A candidate structure for the HIV-1 binding site on the CD4 protein was identified by epitope mapping with a family of eight functionally distinct CD4-specific monoclonal antibodies in conjunction with a panel of large CD4-derived synthetic peptides. All of the seven epitopes that were located reside within two immunoglobulin-like disulfide loops situated between residues 1 and 168 of the CD4 protein. The CD4-specific monoclonal antibody OKT4A, a potent inhibitor of HIV-1 binding, recognized a site between residues 32 and 47 on the CD4 protein. By analogy to other members of the immunoglobulin superfamily of proteins, this particular region has been predicted to exist as a protruding loop. A synthetic analog of this loop (residues 25 to 58) showed a concentration-dependent inhibition of HIV-1-induced cell %%%fusion%%% . It is proposed that a loop extending from residues 37 to 53 of the CD4 protein is a binding site for the AIDS virus.

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02642988 79153202
Scoliosis and hydrocephalus in myelocele patients. The effects of ventricular shunting.
Hall P; Lindseth R; %%%Campbell R%%%; Kalsbeck JE; Desousa A J Neurosurg (UNITED STATES) Feb 1979, 50 (2) p174-8, ISSN 0022-3085 Journal Code: JD3
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Developmental scoliosis is a common cause of increasing disability and deformity in long-term myelocele survivors, and is believed to result from a paralytic collapsing spine. The possible etiological role of compensated hydrocephalus and hydromyelia was assessed by determining the effect of ventricular shunting on 11 myelocele patients with developmental scoliosis. After successful shunting, one patient with a 47 degrees curve continued to deteriorate. Three cases with curves greater than 60 degrees were stabilized for short periods, but eventually required spinal %%%fusion%%%. Seven cases with curves less than 55 degrees were improved from a mean scoliosis of 29 degrees to 13 degrees during a 20-month follow-up period. Several patients had pre-existing shunts that were found to be non-functional on shuntogram. These findings suggest that the spinal complications of hydrocephalus may be more common than previously recognized in myelocele patients and that advanced developmental scoliosis may be avoided by early recognition and ventricular shunting. ? ds

Set	Items	Description
S1	274	E3, E6
S2	141	E3-E7
S3	3	S1 AND S2
S4	255	E3,E16
S5	84	E3,E4
S6	48	E3,E4
S7	387	S4 OR S5 OR S6
S8	3	S7 AND HYBRID
S9	11	S7 AND CHIMER?
S10	11	S9 NOT S8
S11	11	S7 AND FUSION NOT (S8 OR S9)

? logout

01may98 15:03:09 User217743 Session D445.5
$3.48 0.116 Hrs File155
$0.20 1 Type(s) in Format 3 (UDF)
$5.40 27 Type(s) in Format 4 (UDF)
$5.60 28 Types
$9.08 Estimated cost File155
$9.08 Estimated cost this search
$113.18 Estimated total session cost 0.323 Hrs.
Logoff: level 98.04.30 D 15:03:09